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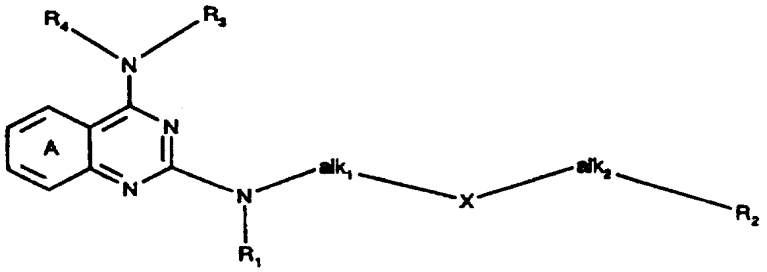
(57) Abstract

The invention relates to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal, including man, in need of such treatment a therapeutically effective amount of a compound of formula (I), in which the variables are as defined and relates to new compounds of formula (I) or a salt thereof, to pharmaceutical compositions, and to the manufacture of new compounds of formula (I) and salts thereof.



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QUINAZOLIN-2,4-DIAZIRINES AS NPY RECEPTOR ANTAGONIST

Background of the Invention

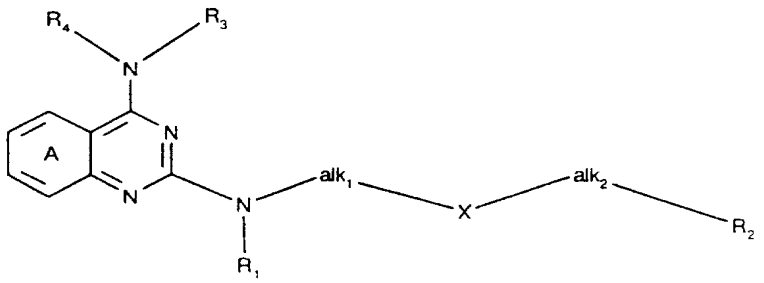
Neuropeptide Y (NPY) is a member of the pancreatic polypeptide family of peptides and is one of the most abundant and widely distributed peptides at the central and peripheral nervous system. NPY acts as a neurotransmitter playing an important role in the regulation of various diseases. Intensive evaluations lead to the finding that multiple NPY receptors are existing being responsible for different physiological and pharmacological activities. Recently, a new NPY receptor subtype has been characterized and cloned, designated as Y5 receptor. It has been demonstrated that the pharmacological function associated with Y5 relates, for example, to obesity and eating disorders. Accordingly, the provision of compounds which act as antagonists of this receptor subtype represents a promisable approach in the regulation of diseases or disorders, such as obesity and eating/food intake disorders.

Summary of the Invention

The invention relates to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5, to pharmaceutical compositions and to new compounds having Y5 antagonistic properties.

Detailed Description of the Invention

The invention relates to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal, including man, in need of such treatment a therapeutically effective amount of a compound of formula (I)



in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R_2 represents

(i) hydrogen, halogen, nitro, cyano, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, by lower alkoxy, by amino, by substituted amino, by carboxy, by lower alkoxycarbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl, by carbamoyl, or by N-substituted carbamoyl;

(ii) amino or substituted amino;

(iii) hydroxy, lower alkoxy, lower alkenyloxy, lower alkynyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C_3-C_8-cycloalkoxy, C_3-C_8-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl-oxy, aminocarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) carbamoyl or N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-O-R, -NR_1-CO-R, -NR_1-CO-NR_1-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X_1(X_2)(X_3) wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula -X_4-$(CO)_p$-$(CH_2)_o$-, -$(CH_2)_q$-X_4-$(CO)_p$-$(CH_2)_r$-, or -$(CH_2)_s$-X_4-CO-$(CH_2)_t$-; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula -CO-$(CH_2)_u$-; [X_4 being -CH_2-, -N(R_1)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from -CH_2-;];

R_3 and R_4 , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, N-substituted carbamoyl, and -$S(O)_n$-R;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents (carbocyclic or heterocyclic) arylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of
(i) halogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, lower alkynyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, (carbocyclic or heterocyclic) aroyl, nitro, cyano;
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iv) amino, substituted amino;
(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen, lower alkyl, lower alkenyl, lower alkinyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO_2-R, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy;

wherein, in each case, R represents hydrogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy; or a pharmaceutically accetable salt thereof; and relates to new compounds of formula (I) or a salt thereof, to pharmaceutical compositions, and to the manufacture of new compounds of formula (I) and salts thereof.

The compounds of formula (I) can be present as salts, in particular pharmaceutically acceptable salts. If the compounds (I) have, for example, at least one basic centre, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, a phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as C_1-C_4-alkanecarboxylic acids which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, for example aspartic or glutamic acid, or such as benzoic acid, or with organic sulfonic acids, such as C_1-C_4-alkane- or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methane- or p-toluenesulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an

additionally present basic centre. The compounds (I) having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine, or a mono-, di- or trihydroxy lower alkylamine, for example, mono-, di- or triethanolamine. Corresponding internal salts may furthermore be formed, if a compound of formula comprises e.g. both a carboxy and an amino group. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds (I) or their pharmaceutically acceptable salts, are also included.

(Carbocyclic or heterocyclic) aryl in (carbocyclic or heterocyclic) aryl or aryloxy, respectively, represents, for example, phenyl, biphenylyl, naphthyl or an appropriate 5- or 6-membered and monocyclic radical or an appropriate bicyclic heteroaryl radical which, in each case, have up to four identical or different hetero atoms, such as nitrogen, oxygen or sulfur atoms, preferably one, two, three or four nitrogen atoms, an oxygen atom or a sulfur atom. Appropriate 5-membered heteroaryl radicals are, for example, monoaza-, diaza-, triaza-, tetraaza-, monooxa- or monothia-cyclic aryl radicals, such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl and thienyl, while suitable appropriate 6-membered radicals are in particular pyridyl. Appropriate bicyclic heterocyclic aryls are, for example, indolyl, indazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinolinyl, isoquinolinyl, or quinazolinyl. Appropriate aromatic radicals, including ring A, are radicals which may be monosubstituted or polysubstituted, for example di- or trisubstituted, for example by identical or different radicals, for example selected from the group as given above. Preferred substituents of corresponding aryl radicals (including of ring A) are, for example, halogen, lower alkyl, halo-lower alkyl, lower alkoxy, oxy-lower alkylene-oxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

(Carbocyclic or heterocyclic) aroyl is in particular benzoyl, naphthoyl, furoyl, thenoyl, or pyridoyl.

(Carbocyclic or heterocyclic) aryl-lower alkanoyl in (carbocyclic or heterocyclic) aryl-lower alkanoyloxy or (carbocyclic or heterocyclic) aryl-lower alkanoyl is in particular phenyl-lower alkanoyl, naphthyl-lower alkanoyl, or pyridyl-lower alkanoyl.

(Carbocyclic or heterocyclic) aryl-lower alkyl is in particular phenyl-, naphthyl- or pyridyl-lower alkyl.

(Carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl is in particular phenyl-, naphthyl- or pyridyl-lower alkoxy.

(Carbocyclic or heterocyclic) arylene represents, in particular, phenylene, naphthylene, thiophenylene, furylene, pyridylene which may be substituted, for example, as indicated for benzo ring A or preferably unsubstituted.

Lower alkyl which substituted by halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, or amino is in particular halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, phenyloxy-, naphthyloxy- or pyridyloxy-lower alkyl, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl, amino-lower alkyl, or N- or N,N- substituted amino-lower alkyl.

An amino group which is mono-substituted by lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl is in particular lower alkylamino, C_3-C_8-cycloalkyl-amino, C_3-C_8-cycloalkyl-loweralkyl-amino, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-amino, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkylamino.

An amino group which is, independently of one another, di-substituted by lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl is in particular di-lower alkylamino, di-C_3-C_8-cycloalkyl-amino, di-(C_3-C_8-cycloalkyl-lower alkyl)-amino, di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-amino, di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino, lower alkyl-C_3-C_8-cycloalkyl-amino, lower alkyl-(C_3-C_8-cycloalkyl-lower alkyl)-amino, lower alkyl-(phenyl-,

naphthyl-, furyl-, thienyl-, or pyridyl)-amino, lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino.

Lower alkyl which is substituted by carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, carbamoyl in which the amino group is mono-substituted or, independently of one another, di-substituted by lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, and carbamoyl in which the amino group is di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$, NR_0, the integer n being 0, 1 or 2 and R_0 being hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, $-SO_3H$, $-SO_2$-R and R being lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl] is in particular carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, lower alkoxy-lower alkoxy-carbonyl-lower alkyl, (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl, or corresponding N- or N,N-substituted carbamoyl-lower alkyl.

Lower alkoxy which substituted by halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, or amino is in particular halo-lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, phenyloxy-, naphthyloxy- or pyridyloxy-lower alkyl, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkoxy, amino-lower alkoxy, or corresponding N- or N,N- substituted amino-lower alkoxy.

Lower alkoxy which is substituted by carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, carbamoyl in which the amino group is mono-substituted or, independently of one another, di-substituted by lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, and carbamoyl in which the amino group is di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$, NR_0, the integer n being 0, 1 or 2 and R_0 being hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, $-SO_3H$, $-SO_2$-R and R being lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-

lower alkyl] is in particular carboxy-lower alkoxy, lower alkoxy-carbonyl-lower alkoxy, lower alkoxy-lower alkoxy-carbonyl-lower alkoxy, (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy, N- or N,N-substituted carbamoyl-lower alkoxy.

Substituted lower alkyl or lower alkoxy, respectively, is mono- or poly-substituted, e.g. di- or tri-substituted.

The group of formula -N(R_3)(R_4) in which R_3 and R_4 together represent lower alkylene which is condensedat two adjacent carbon atoms with a benzene ring represents, for example, lower alkylene-phenylene-lower alkylene-amino, such as 3,4-dihydro-1*H*-isoquinolin-2-yl.

The general definitions used above and below, unless defined differently, have the following meanings:

The expression "lower" means that corresponding groups and compounds, in each case, in particular comprise not more than 7, preferably not more than 4, carbon atoms.

Halogen is in particular halogen of atomic number not more than 35, such as fluorine, chlorine or bromine, and also includes iodine.

Lower alkyl is in particular C_1-C_7- alkyl, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, and also includes corresponding pentyl, hexyl and heptyl radicals. C_1-C_4-alkyl is preferred.

Lower alkenyl is in particular C_3-C_7-alkenyl and is, for example, 2-propenyl or 1-, 2- or 3-butenyl. C_3-C_5-alkenyl is preferred.

Lower alkynyl is in particular C_3-C_7-alkynyl and is preferably propargyl.

Lower alkoxy is in particular C_1-C_7-alkoxy and is, for example, methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy and also includes corresponding pentyloxy, hexyloxy and heptyloxy radicals. C_1-C_4-

alkoxy is preferred.

Lower alkenyloxy is in particular C_3-C_7-alkenyloxy, preferably allyloxycarbonyl, while lower alkynyloxy is in particular C_3-C_5-alkynyloxy, such as propargyloxy.

Oxy-lower alkylene-oxy is in particular oxy-C_1-C_4-alkylene-oxy, preferably oxy-methylene-oxy or oxy-ethylene-oxy.

Lower alkanoyloxy is in particular C_2-C_7-alkanoyloxy, such as acetyloxy, propionyloxy, butyryloxy, isobutyryloxy or pivaloyloxy. C_2-C_5-alkanoyloxy is preferred.

Lower alkanoyl is in particular C_2-C_7-alkanoyl, such as acetyl, propionyl, butyryl, isobutyryl or pivaloyl. C_2-C_5-alkanoyl is preferred.

Naphthoyl is 1- or 2-naphthoyl, furoyl 2- or 3-furoyl, thenoyl 2- or 3-thenyl, and pyridoyl 2-, 3-, or 4-pyridoyl.

C_3-C_8-Cycloalkyl is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Cyclopentyl and cyclohexyl are preferred.

C_3-C_8-Cycloalkyl-lower alkyl is in particular C_3-C_8-cycloalkyl-C_1-C_4-alkyl, in particular C_3-C_6-cycloalkyl-C_1-C_2-alkyl. Preferred is cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl.

C_3-C_8-Cycloalkoxy is, for example, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy. Cyclopentyloxy and cyclohexyloxy are preferred.

C_3-C_8-Cycloalkyl-lower alkoxy is in particular C_3-C_8-cycloalkyl-C_1-C_4-alkoxy, in particular C_3-C_6-cycloalkyl-C_1-C_2-alkoxy. Preferred is cyclopropylmethoxy, cyclopentylmethoxy or cyclohexylmethoxy.

Lower alkylene is in particular C_1-C_7-alkylene, in particular C_1-C_5-alkylene, and is straight-chain or branched and is in particular methylene, ethylene, propylene and

butylene and also 1,2-propylene, 2-methyl-1,3-propylene, 3-methyl-1,5-pentylene and 2,2-dimethyl-1,3-propylene. C_3-C_5-alkylene is preferred. In case of alk_1 or alk_2, respectively, lower alkylene preferably is $-(CH_2)_p-$ the integer p being 1-3. Lower alkylene in an substituted amino group preferably is 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1,5-pentylene, 1,6-hexylene, 2-methyl-1,3-propylene, or 2-methyl-butylene, or 3-methyl-1,5-pentylene.

Amino which is di-substituted by lower alkylene is in particular C_3-C_7-alkyleneamino, preferably 1-azidino, 1-pyrrolidino or 1-piperidino.

Amino which is di-substituted by lower alkylene which is interrupted by O, $S(O)_n$ or NR_0 is in particular morpholino, thiomorpholino or the mono- or di-oxide thereof, or 4-R_0-piperazino.

Lower alkanesulfonyl is in particular C_1-C_4-alkoxy-C_1-C_5-alkoxycarbonyl, preferably ethoxyethoxycarbonyl, methoxyethoxycarbonyl and isopropyloxyethoxycarbonyl.

Lower alkoxycarbonyl is in particular C_2-C_8-alkoxycarbonyl and is, for example, methoxy-, ethoxy-, propyloxy- or pivaloyloxy-carbonyl. C_2-C_5-alkoxycarbonyl is preferred.

Lower alkoxy-lower alkoxy-carbonyl is in particular C_1-C_4-alkoxy-C_2-C_5-alkoxycarbonyl and is, for example, methoxy- or ethoxy-ethoxy-alkoxycarbonyl.

Hydroxy-lower alkyl is in particular hydroxy-C_1-C_4-alkyl, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl. Furthermore, hydroxy-lower alkyl may exhibit two hydroxy groups, such as 3-hydroxy-1-hydroxymethyl-propyl.

Hydroxy-lower alkoxy is in particular hydroxy-C_1-C_4-alkoxy, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl.

Lower alkoxy-lower alkoxy is in particular C_1-C_4-alkoxy-C_1-C_4-alkoxy and is, for example, (m)ethoxymethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 2-n-propyloxyethoxy or ethoxymethoxy.

Amino which is di-substituted by lower alkylene and is condensed at two adjacent carbon atoms with a benzene ring is in particular C_2-C_6-cycloalkylenemino which is condensed at two adjacent carbon atoms with a benzene ring. Preferred is indolin-1-yl or 1,2,3,4-tetrahydro-quinolin-1-yl.

Halo-lower alkyl is in particular halo-C_1-C_4-alkyl, such as trifluoromethyl, 1,1,2-trifluoro-2-chloroethyl or chloromethyl.

Halo-lower alkoxy is in particular halo-C_1-C_4-alkoxy, such as trifluoromethoxy, 1,1,2-trifluoro-2-chloroethoxy or chloromethoxy.

Phenyloxy-, naphthyloxy- or pyridyloxy-lower alkyl is in particular phenyloxy-, naphthyloxy- or pyridyloxy-C_1-C_4-alkyl, such as phenoxy-methyl, 2-phenoxy-ethyl, 1- or 2-naphthyloxy-methyl, or 2-, 3-, or 4-pyridyloxy-methyl.

Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl is in particular phenyl-, naphthyl- or pyridyl-C_1-C_4-alkyl, such as phenyl-methyl, 2-phenyl-ethyl, 1- or 2-naphthyl-methyl, or 2-, 3-, or 4-pyridyl-methyl.

Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkoxy is in particular phenyl-, naphthyl- or pyridyl-C_1-C_4-alkoxy, such as phenyl-methoxy, 2-phenyl-ethoxy, 1- or 2-naphthyl-methoxy, or 2-, 3-, or 4-pyridyl-methoxy.

Naphthyl is in particular 1- or 2-naphthyl; furyl 2- or 3-furyl; thienyl 2- or 3-thienyl; pyridyl 2-, 3- or 4-pyridyl, indolyl e.g. 1-, 2-, 3- or 5-indolyl, indazolyl e.g. 6-1(H)-indazolyl, benzofuranyl e.g. 2-, 3- or 5-benzofuranyl, benzothienyl e.g. 2-, 3-, or 5-benzothienyl, benzimidazolyl e.g. 1-, 2- or 5-benzimidazolyl, quinolinyl e.g. 2-, 4-, 5-, 6-, 7-, or 8-quinolinyl, isoquinolinyl e.g. 1-, 3-, 4-, or 6-isoquinolyl, or quinazolinyl e.g. 2-, 4-, 5-, 6-, 7-, or 8-quinazolinyl.

Amino-lower alkyl is in particular amino-C_1-C_7-alkyl, preferably amino-C_1-C_4-alkyl, such as aminomethyl, 2-aminoethyl or 3-aminopropyl.

Lower alkylamino is in particular C_1-C_7-alkylamino and is, for example, methyl-, ethyl-, n-propyl- and isopropyl-amino. C_1-C_4-alkylamino is preferred.

C_3-C_8-Cycloalkyl-amino is in particular C_3-C_6-cycloalkyl-amino and is, for example, cyclopropyl-, cyclopentyl- and cyclohexyl-amino.

C_3-C_8-Cycloalkyl-lower alkylamino is in particular C_3-C_8-cycloalkyl-C_1-C_7-alkylamino and is, for example, cyclopropylmethyl-amino or cyclohexylmethyl-amino. C_3-C_8-Cycloalkyl-C_1-C_4-alkylamino is preferred.

Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl-amino is in particular phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-C_1-C_4-alkyl-amino, preferably benzyl-amino, 2-phenethyl-amino, 1- or 2-naphthylmethyl-amino, or 2-, 3-, or 4-pyridylmethyl-amino.

Di-lower alkylamino is in particular di-C_1-C_4-alkylamino, such as dimethyl-, diethyl-, di-n-propyl-, methylpropyl-, methylethyl-, methylbutyl-amino and dibutylamino.

Di-C_3-C_8-cycloalkyl-amino is in particular di-C_3-C_6-cycloalkylamino, preferably cyclopropylamino, cyclopentylamino or cyclohexylamino.

Di-(C_3-C_8-cycloalkyl-lower alkyl)-amino is in particular di-(C_3-C_6-cycloalkyl-C_1-C_4-alkyl)-amino, preferably cyclopropylmethyl-amino, cyclopentylmethyl-amino or cyclohexylmethyl-amino.

Di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino is in particular di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-C_1-C_4- alkyl)-amino, preferably di-benzyl-amino, di-(2-phenethyl)-amino, di-(1- or 2-naphthylmethyl)-amino, or di-(2-, 3-, or 4-pyridylmethyl)-amino.

Lower alkyl-C_3-C_8-cycloalkyl-amino is in particular C_1-C_4-alkyl-C_3-C_6-cycloalkyl-amino, preferably methyl-cyclopropyl-amino, methyl-cyclopentyl-amino or methyl-cyclohexyl-amino.

Lower alkyl-(C_3-C_8-cycloalkyl-lower alkyl)-amino is in particular C_1-C_4-alkyl-(C_3-C_6-cycloalkyl-C_1-C_4-alkyl)amino, preferably methyl-cyclopropylmethyl-amino, methyl-cyclopentylmethyl-amino or methyl-cyclohexylmethyl-amino.

Lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)- amino is in particular C_1-C_4-alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)- amino, such as (m)ethyl-phenyl-amino.

Lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino is in particular C_1-C_4-alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-C_1-C_4-alkyl)-amino, such as (m)ethyl-benzyl-amino or (m)ethyl-(2-phenethyl)-amino.

Carboxy-lower alkyl is in particular carboxy-C_1-C_4-alkyl, such as carboxy-methyl, 2-carboxy-ethyl, or 3-carboxy-propyl.

Lower alkoxy-carbonyl-lower alkyl is in particular C_2-C_5-alkoxycarbonyl-C_1-C_4-alkyl, such as (m)ethoxycarbonyl-methyl, 2-(m)ethoxycarbonyl-ethyl or 2-pivaloyl-ethyl.

Lower alkoxy-lower alkoxy-carbonyl-lower alkyl is in particular C_1-C_4-alkoxy-C_2-C_5-alkoxycarbonyl-C_1-C_4-alkyl, such as 2-methoxy-ethoxycarbonyl-methyl or 2-(2-ethoxy-ethoxycarbonyl)-ethyl.

(Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxycarbonyl-lower alkyl is in particular (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-C_2-C_5-alkoxycarbonyl-C_1-C_4-alkyl, such as benzyloxycarbonyl-methyl or 2-(2-phenethyloxy-carbonyl)-ethyl.

Carbamoyl-lower alkyl is in particular carbamoyl-C_1-C_4-alkyl, such as carbamoyl-methyl, 2-carbamoyl-ethyl or 3-carbamoyl-propyl.

Amino-lower alkoxy is in particular amino-C_1-C_4-alkoxy, such as aminomethoxy, 2-aminoethoxy, or 3-amino-propoxy.

Carboxy-lower alkoxy is in particular carboxy-C_1-C_4-alkoxy, such as carboxy-methoxy, 2-carboxy-ethoxy, or 3-carboxy-propyloxy.

Lower alkoxy-carbonyl-lower alkoxy is in particular C_2-C_5-alkoxycarbonyl-C_1-C_4-alkoxy, such as (m)ethoxycarbonyl-methoxy, 2-methoxycarbonyl-ethyl, or 2-(2-ethoxycarbonyl)-ethyl.

Lower alkoxy-lower alkoxy-carbonyl-lower alkoxy is in particular C_1-C_4-alkoxy-C_2-C_5-alkoxycarbonyl-C_1-C_4-alkoxy, such as (m)ethoxymethoxycarbonyl-methoxy, 2-ethoxy-methoxycarbonyl-ethyl, or 2-[(2-ethoxy-ethoxycarbonyl)]-ethyl.

(Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxycarbonyl-lower alkoxy is in particular (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-C_2-C_5-alkoxycarbonyl-C_1-C_4-alkoxy, such as benzyloxycarbonyl-methoxy, phenethyloxycarbonyl-methoxy, 2-(benzyloxycarbonyl)-ethoxy, or 2-(2-phenethyloxycarbonyl)-ethoxy.

Carbamoyl-lower alkoxy is in particular carbamoyl-C_1-C_4-alkoxy, such as carbamoyl-methoxy, 2-carbamoyl-ethoxy, or 3-carbamoyl-propyloxy.

Phenylene is 1,2-, 1,3 or preferably 1,4-phenylene; naphthylene is in particular 1,2-, 1-3-, 1,4-, 2,4-, 1,5-, or 2,7-naphthylene, furylene is in particular 2,3-, 2,4- or 3,4-furylene, thienylene is in particular 2,3-, 2,4- or 3,4-thienylene, pyridylene is in particular 2,3- or 2,4-pyridylene.

Obesity, for example, is a wide-spread phenomena which e.g. causes a variety of pathological symptoms or influences the overall state of health. Also associated therewith are considerable socio-economic investments and a heavy financial burden for managed health care organisations. The problem to be solved is to present an approach to systemically treat obesity or related diseases or disorders. Surprisingly, it has been manifested that the modulation of the NPY receptor subtype Y5 leads to a control of the eating behavior.

Extensive pharmacological investigations have shown that the compounds (I) and their pharmaceutically acceptable salts, for example, are useful as antagonists of the neuropeptide Y5 receptor subtype.

Neuropeptide Y (NPY) is a member of the pancreatic polypeptide family with wide-spread distribution throughout the mammalian nervous system. NPY and its relatives (peptide YY or PYY, and pancreatic polypeptide or PP) elicit a broad range of physiological effects through activation of at least five G protein-coupled receptor subtypes known as Y1, Y2, Y3, Y4 (or PP), and the "atypical Y1". The role of NPY as the most powerful stimulant of feeding behavior yet described is thought to occur primarily through activation of the hypothalamic "atypical Y1" receptor. This receptor is unique in that its classification is based solely on feeding behavior data, rather than radioligand binding data, unlike the Y1, Y2, Y3, and Y4 (or PP) receptors, each of which are described previously in both radioligand binding and functional assays. ^{125}I-PYY-based expression cloning technique may be used to isolate a rat hypothalamic cDNA encoding an "atypical Y1" receptor referred to herein as the Y5 subtype. Y5 homolog may be isolated and characterized of from human hippocampus. Protein sequence analysis reveals that the Y5 receptor belongs to the G protein- coupled receptor superfamily. Both the human and rat homolog display $\leq$ 42% identity in transmembrane domains with the previously cloned "Y-type" receptors. Rat brain localization studies using in situ hybridization techniques verify the existence of Y5 receptor mRNA in rat hypothalamus. Pharmacological evaluation reveals the following similarities between the Y5 and the "atypical Y1" receptor. 1) Peptides bind to the Y5 receptor with a rank order of potency identical to that described for the feeding response: NPY ^{3} NPY_{2-36} = PYY = [Leu^{31}, Pro^{34}]NPY >> NPY_{13-36}. 2) The Y5 receptor is negatively coupled to cAMP accumulation, as has been proposed for the "atypical Y1" receptor. 3) Peptides activate the Y5 receptor with a rank order of potency identical to that described for the feeding response. 4) The reported feeding "modulator" [D-Trp^{32}]NPY binds selectively to the Y5 receptor and subsequently activated the receptor. 5) Both the Y5 and the "atypical Y1" receptors are sensitive to deletions or modifications in the midregion of NPY and related peptide ligands.

The peptide neurotransmitter neuropeptide Y (NPY) is a 36 amino acid member of the pancreatic polypeptide family with widespread distribution throughout the mammalian nervous system. NPY is considered to be the most powerful stimulant of feeding behavior yet described (Clark, J.T., Kalra, P.S., Crowley, W.R., and Kalra, S.P. (1984). Neuropeptide Y and human pancreatic polypeptide stimulate feeding behavior in rats. Endocrinology 115: 427-429, 1984; Levine, A.S., and Morley, J.E. (1984). Neuropeptide Y: A potent inducer of consummatory behavior in rats. Peptides 5: 1025-1029; Stanley, B.G., and Leibowitz, S.F.; (1984) Neuropeptide Y: Stimulation of feeding and drinking by injection into the paraventricular nucleus. Life Sci. 35: 2635-2642). Direct injection into the hypothalamus of satiated rats, for example,

can increase food intake up to 10-fold over a 4-hour period (Stanley, B.G., Magdalin, W., Seirafi, A., Nguyen, M.M., and Leibowitz, S.F. (1992). Evidence for neuropeptide Y mediation of eating produced by food deprivation and for a variant of the Y_1 receptor mediating this peptide's effect. Peptides 13: 581-587). The role of NPY in normal and abnormal eating behavior, and the ability to interfere with NPY-dependent pathways as a means to appetite and weight control, are areas of great interest in pharmacological and pharmaceutical research (Sahu and Kalra, 1993; Dryden, S., Frankish, H., Wang, Q., and Williams, G. (1994). Neuropeptide Y and energy balance: one way ahead for the treatment of obesity? Eur. J. Clin. Invest. 24: 293-308). Any credible means of studying or controlling NPY-dependent feeding behavior, however, must necessarily be highly specific as NPY can act through at least 5 pharmacologically defined receptor subtypes to elicit a wide variety of physiological functions (Dumont, Y., J.-C. Martel, A. Fournier, S. St-Pierre, and R. Quirion. (1992). Neuropeptide Y and neuropeptide Y receptor subtypes in brain and peripheral tissues. Progress in Neurobiology 38: 125-167). It is therefore vital that knowledge of the molecular biology and structural diversity of the individual receptor subtypes be understood as part of a rational drug design approach to develop subtype selective compounds. A brief review of NPY receptor pharmacology is summarized below and also in Table 1.

TABLE 1: Pharmacologically defined receptors for NPY and related pancreatic polypeptides.

Rank orders of affinity for key peptides (NPY, PYY, PP, [Leu^{31},Pro^{34}]NPY, NPY_{2-36}, and NPY_{13-36}) are based on previously reported binding and functional data (Schwartz, T.W., J. Fuhlendorff, L.L.Kjems, M.S. Kristensen, M. Vervelde, M. O'Hare, J.L. Krstenansky, and B. Bjornholm. (1990). Signal epitopes in the three-dimensional structure of neuropeptide Y. Ann. N.Y. Acad. Sci. 611: 35-47; Wahlestedt, C., Karoum, F., Jaskiw, G., Wyatt, R.J., Larhammar, D., Ekman, R., and Reis, D.J. (1991). Cocaine-induced reduction of brain neuropeptide Y synthesis dependent on medial prefrontal cortex. Proc. Natl. Acad. Sci. 88: 2978-2082; Dumont, Y., J.-C. Martel, A. Fournier, S. St-Pierre, and R. Quirion. (1992). Neuropeptide Y and neuropeptide Y receptor subtypes in brain and peripheral tissues. Progress in Neurobiology 38: 125-167; Wahlestedt, C., and D.J. Reis. (1993). Neuropeptide Y-Related Peptides and Their Receptors--Are the Receptors Potential Therapeutic Targets? Ann. Rev. Pharmacol. Tox. 32: 309-352). Missing peptides in the series reflect a lack of published information.

TABLE 1

Receptor	Affinity (pK_i or pEC_{50})					
	11 to 10	10 to 9	9 to 8	8 to 7	7 to 6	< 6
Y1	NPY PYY [Leu^{31},Pro^{34}] NPY		NPY_{2-36}	NPY_{13-36}	PP	
Y2		PYY NPY NPY_{2-36}	NPY_{13-36}			[Leu^{31},Pro^{34}] NPY PP
Y3		NPY	[Pro^{34}] NPY	NPY_{13-36}PP		PYY
Y4	PP	PYY [Leu^{31},Pro^{34}] NPY	NPY NPY_{2-36}	NPY_{13-36}		
Y5		PYY NPY NPY_{2-36} [Leu^{31},Pro^{34}] NPY		NPY_{13-36}		

NPY Receptor Pharmacology

NPY receptor pharmacology has historically been based on structure/activity relationships within the pancreatic polypeptide family. The entire family includes the namesake pancreatic polypeptide (PP), synthesized primarily by endocrine cells in the pancreas; peptide YY (PYY), synthesized primarily by endocrine cells in the gut; and NPY, synthesized primarily in neurons (Michel, M.C. (1991). Receptors for neuropeptide Y: multiple subtypes and multiple second messengers. Trends Pharmacol.: 12: 389-394; Dumont et al., 1992; Wahlestedt and Reis, 1993). All pancreatic polypeptide family members share a compact structure involving a "PP-fold" and a conserved C-terminal hexapeptide ending in Tyr^{36} (or Y^{36} in the single letter code). The striking conservation of Y^{36} has prompted the reference to the pancreatic polypeptides' receptors as "Y-type" receptors (Wahlestedt, C., L. Edvinsson, E. Ekblad, and R. Hakanson. Effects of neuropeptide Y at sympathetic neuroeffector junctions: Existence of Y_1 and Y_2 receptors. In: Neuronal messengers in vascular function, Fernstrom Symp. No 10., pp. 231-242. Eds A. Nobin and C.H. Owman. Elsevier: Amsterdam (1987)), all of which are proposed to function as seven transmembrane-spanning G protein-coupled receptors (Dumont et al., 1992).

The Y1 receptor recognizes NPY = PYY >> PP (Grundemar et al., 1992). The receptor requires both the N- and the C-terminal regions of the peptides for optimal recognition. Exchange of Gln^{34} in NPY or PYY with the analogous residue from PP (Pro^{34}), however, is well-tolerated. The Y1 receptor has been cloned from a variety of species including human, rat and mouse (Larhammar, D., A.G. Blomqvist, F. Yee, E. Jazin, H. Yoo, and C. Wahlestedt. (1992). Cloning and functional expression of a human neuropeptide Y/peptide YY receptor of the Y1 type. J. Biol. Chem. 267: 10935-10938; Herzog, H., Y.J. Hort, H.J. Ball, G. Hayes, J. Shine, and L. Selbie. (1992). Cloned human neuropeptide Y receptor couples to two different second messenger systems. Proc. Natl. Acad. Sci. USA 89, 5794-5798; Eva, C., Oberto, A., Sprengel, R. and E. Genazzani. (1992). The murine NPY-1 receptor gene: structure and delineation of tissue specific expression. FEBS lett. 314: 285-288; Eva, C., Keinanen, K., Monyer, H., Seeburg, P., and Sprengel, R. (1990). Molecular cloning of a novel G protein-coupled receptor that may belong to the neuropeptide receptor family. FEBS Lett. 271, 80-84). The Y2 receptor recognizes PYY ~ NPY >> PP and is relatively tolerant of N-terminal deletion (Grundemar, L. and RI Hakanson (1994). Neuropeptide Y effector systems:

perspectives for drug development. Trends. Pharmacol. 15:153-159). The receptor has a strict requirement for structure in the C-terminus (Arg^{33}-Gln^{34}-Arg^{35}-Tyr^{36}-NH_2); exchange of Gln^{34} with Pro^{34}, as in PP, is not well tolerated. The Y2 receptor has recently been cloned. The Y3 receptor is characterized by a strong preference for NPY over PYY and PP (Wahlestedt, C., Karoum, F., Jaskiw, G., Wyatt, R.J., Larhammar, D., Ekman, R., and Reis, D.J. (1991). Cocaine-induced reduction of brain neuropeptide Y synthesis dependent on medial prefrontal cortex. Proc. Natl. Acad. Sci. 88: 2978-2082). [Pro^{34}]NPY is reasonably well tolerated even though PP, which also contains Pro^{34}, does not bind well to the Y3 receptor. This receptor (Y3) has not yet been cloned. The Y4 receptor binds PP > PYY > NPY. Like the Y1, the Y4 requires both the N- and the C-terminal regions of the peptides for optimal recognition. The "atypical Y1" or "feeding" receptor is defined exclusively by injection of several pancreatic polypeptide analogs into the paraventricular nucleus of the rat hypothalamus which stimulates feeding behavior with the following rank order: $NPY_{2-36} \geq$ NPY ~ PYY ~ [Leu^{31},Pro^{34}]NPY > NPY_{13-36} (Kalra, S.P., Dube, M.G., Fournier, A., and Kalra, P.S. (1991). Structure-function analysis of stimulation of food intake by neuropeptide Y: Effects of receptor agonists. Physiology & Behavior 50: 5-9; Stanley, B.G., Magdalin, W., Seirafi, A., Nguyen, M.M., and Leibowitz, S.F. (1992). Evidence for neuropeptide Y mediation of eating produced by food deprivation and for a variant of the Y_1 receptor mediating this peptide's effect. Peptides 13: 581-587). The profile is similar to that of a Y1-like receptor except for the anomalous ability of NPY_{2-36} to stimulate food intake with potency equivalent or better than that of NPY. A subsequent report by Balasubramaniam, A., Sheriff, S., Johnson, M.E., Prabhakaran, M., Huang, Y., Fischer, J.E., and Chance, W.T. (1994). [$D\text{-}Trp^{32}$]Neuropeptide Y: A competitive antagonist of NPY in rat hypothalamus. J. Med. Chem. 37: 311-815 showed that feeding can be regulated by [$D\text{-}Trp^{32}$]NPY. While this peptide is presented as an NPY antagonist, the published data at least in part support a stimulatory effect of [$D\text{-}Trp^{32}$]NPY on feeding. [$D\text{-}Trp^{32}$]NPY thereby represents another diagnostic tool for receptor identification.

This plasmid (pcEXV-hY5) was deposited on November 4, 1994 with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorgansims for the Purposes of Patent Procedure and was accorded ATCC Accession No. 75943.

The plasmid which comprises the regulatory elements necessary for expression of DNA in a mammalian cell operatively linked to the DNA encoding the rat Y5 receptor as to permit expression thereof has been designated as pcEXV-rY5 (ATCC Accession No. 75944).

This plasmid (pcEXV-rY5) was deposited on November 4, 1994 with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorgansims for the Purposes of Patent Procedure and was accorded ATCC Accession No. CRL 75944.

A method for determining whether a ligand can specifically bind to a Y5 receptor comprises contacting a cell transfected with and expressing DNA encoding the Y5 receptor with the ligand under conditions permitting binding of ligands to such receptor, detecting the presence of any such ligand specifically bound to the Y5 receptor, and thereby determining whether the ligand specifically binds to the Y5 receptor.

A method for determining whether a ligand is a Y5 receptor antagonist comprises contacting a cell transfected with and expressing DNA encoding a Y5 receptor with the ligand in the presence of a known Y5 receptor agonist, such as PYY or NPY, under conditions permitting the activation of a functional Y5 receptor response, detecting a decrease in Y5 receptor activity, and thereby determining whether the ligand is a Y5 receptor antagonist.

In an embodiment of the above-described methods, the cell is non-neuronal in origin. In a further embodiment, the non-neuronal cell is a COS-7 cell, 293 human embryonic kidney cell, NIH-3T3 cell or L-M(TK-) cell.

The cell lines are transfected with a vector which is adapted for expression in a mammalian cell which comprises the regulatory elements necessary for expression of the DNA in the mammalian cell operatively linked to the DNA encoding the mammalian Y5 receptor as to permit expression thereof.

For example, such plasmid which comprises the regulatory elements necessary for expression of DNA in a mammalian cell operatively linked to the DNA encoding the human

Y5 receptor as to permit expression thereof designated pcEXV-hY5 (ATCC Accession No. 75943).

Experimental Details

MATERIALS AND METHODS

cDNA Cloning

Total RNA was prepared by a modification of the guanidine thiocyanate method (Kingston, 1987), from 5 grams of rat hypothalamus (Rockland, Gilbertsville, PA). Poly A^+RNA was purified with a FastTrack kit (Invitrogen Corp., San Diego, CA). Double stranded (ds) cDNA was synthesized from 7 mg of poly A^+ RNA according to Gubler and Hoffman (Gubler, U abd B.J. Hoffman. (1983). A simple and very efficient method for generating cDNA libraries. Gene. 25, 263-269), except that ligase was omitted in the second strand cDNA synthesis. The resulting DS cDNA was ligated to BstxI/EcoRI adaptors (Invitrogen Corp.), the excess of adaptors was removed by chromatography on Sephacryl 500 HR (Pharmacia®-LKB) and the ds-cDNA size selected on a Gen-Pak Fax HPLC column (Millipore Corp., Milford, MA). High molecular weight fractions were ligated in pEXJ.BS (A cDNA cloning expression vector derived from pcEXV-3; Okayama, H. and P. Berg (1983). A cDNA cloning vector that permits expression of cDNA inserts in mammalian cells. Mol. Cell. Biol. 3: 280-289; Miller, J. and Germain, R.N. (1986). Efficient cell surface expression of class II MHC molecules in the absence of associated invariant chain. J. Exp. Med. 164: 1478-1489) cut by BstxI as described by Aruffo and Seed (Aruffo, A. and Seed, B. (1987). Molecular cloning of a CD28 cDNA by a high efficiency COS cell expression system. PNAS, 84, 8573-8577). The ligated DNA was electroporated in E.Coli MC 1061 F^+ (Gene Pulser, Biorad). A total of 3.4×10^6 independent clones with an insert mean size of 2.7 kb could be generated. The library was plated on Petri dishes (Ampicillin selection) in pools of 6.9 to 8.2×10^3 independent clones. After 18 hours amplification, the bacteria from each pool were scraped, resuspended in 4 ml of LB media and 1.5 ml processed for plasmid purification with a QIAprep-8 plasmid kit (Qiagen Inc, Chatsworth, CA). 1 ml aliquots of each bacterial pool were stored at -85°C in 20% glycerol.

Isolation of a cDNA clone encoding an atypical rat hypothalamic NPY5 receptor

DNA from pools of » 7500 independent clones was transfected into COS-7 cells by a modification of the DEAE-dextran procedure (Warden, D. and H.V. Thorne. (1968). Infectivity of polyoma virus DNA for mouse embryo cells in presence of diethylaminoethyl-dextran. J. Gen. Virol. 3, 371). COS-7 cells were grown in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal calf serum, 100 U/ml of penicillin, 100 mg/ml of streptomycin, 2 mM L-glutamine (DMEM-C) at 37°C in 5% CO_2. The cells were seeded one day before transfection at a density of 30,000 cells/cm^2 on Lab-Tek chamber slides (1 chamber, Permanox slide from Nunc Inc., Naperville, IL). On the next day, cells were washed twice with PBS, 735 ml of transfection cocktail was added containing 1/10 of the DNA from each pool and DEAE-dextran (500 mg/ml) in Opti-MEM I serum free media (Gibco®BRL LifeTechnologies Inc. Grand Island, NY). After a 30 min. incubation at 37°C, 3 ml of chloroquine (80 mM in DMEM-C) was added and the cells incubated a further 2.5 hours at 37°C. The media was aspirated from each chamber and 2 ml of 10% DMSO in DMEM-C added. After 2.5 min. incubation at room temperature, the media was aspirated, each chamber washed once with 2 ml PBS, the cells incubated 48 hours in DMEM-C and the binding assay was performed on the slides. After one wash with PBS, positive pools were identified by incubating the cells with 1 nM ($3x10^6$ cpm per slide) of porcine [^{125}I]-PYY (NEN; SA=2200 Ci/mmole) in 20 mM Hepes-NaOH pH 7.4, CaCl2 1.26 mM, MgSO4 0.81 mM, KH_2PO_4 0.44 mM, KCL 5.4, NaCl 10 mM, .1% BSA, 0.1% bacitracin for 1 hour at room temperature. After six washes (three seconds each) in binding buffer without ligand, the monolayers were fixed in 2.5% glutaraldehyde in PBS for five minutes, washed twice for two minutes in PBS, dehydrated in ethanol baths for two minutes each (70, 80, 95, 100%) and air dried. The slides were then dipped in 100% photoemulsion (Kodak® type NTB2) at 42°C and exposed in the dark for 48 hours at 4°c in light proof boxes containing drierite. Slides were developed for three minutes in Kodak® D19 developer (32 g/l of water), rinsed in water, fixed in Kodak® fixer for 5 minutes, rinsed in water, air dried and mounted with Aqua-Mount (Lerner Laboratories, Pittsburgh, PA). Slides were screened at 25x total magnification. A single clone, CG-18, was isolated by SIB selection as described (Mc Cormick, 1987). DS-DNA was sequenced with a Sequenase kit (US Biochemical, Cleveland, OH) according to the manufacturer. Nucleotide and peptide sequence analysis were performed with GCG programs (Genetics Computer group, Madison, WI).

Isolation of the human Y5 homolog

Using rat oligonucleotide primers in TM 3 (sense primer; position 484-509 in SEQ ID NO:1) and in TM 6 (antisense primer; position 1219-1243 in SEQ ID NO: 1), a human hippocampal cDNA library has been screened using the polymerase chain reaction. 1 μl (4×10^6 bacteria) of each of 450 amplified pools containing each »5000 independent clones and representing a total of 2.2×10^6 was subjected directly to 40 cycles of PCR and the resulting products analyzed by agarose gel electrophoresis. One of three positive pools was analyzed further and by sib selection a single cDNA clone was isolated and characterized. This cDNA turned out to be full length and in the correct orientation for expression. DS-DNA was sequenced with a sequenase kit (US Biochemical, Cleveland, OH) according to the manufacturer.

Cell Culture

COS-7 cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 mg/ml streptomycin) at 37°C, 5% CO_2. Stock plates of COS-7 cells were trypsinized and split 1:6 every 3-4 days. Human embryonic kidney 293 cells were grown on 150 mm plates in D-MEM with supplements (minimal essential medium) with Hanks' salts and supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 mg/ml streptomycin) at 37 °C, 5% CO_2. Stock plates of 293 cells were trypsinized and split 1:6 every 3-4 days. Mouse fibroblast LMT(k)- cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 mg/ml streptomycin) at 37 °C, 5% CO_2. Stock plates of COS-7 cells were trypsinized and split 1:10 every 3-4 days.

Stable Transfection

Human Y5 and rat Y5 receptors were co-transfected with a G-418 resistant gene into mouse fibroblast LMT(k)- cells by a calcium phosphate transfection method (Cullen, B.

(1987). Use of eurkaryotic expression technology in the functional analysis of cloned genes. Methods Enzymol. 152: 685-704). Stably transfected cells were selected with G-418.

EXPERIMENTAL RESULTS

cDNA Cloning

In order to clone a rat hypothalamic "atypical" NPY receptor subtype, applicants used an expression cloning strategy in COS-7 cells (Gearing et al, 1989; Kluxen, F.W., Bruns, C. and Lubbert H. (1992). Expression cloning of a rat brain somatostatin receptor cDNA. Proc. Natl. Acad. Sci. USA 89, 4618-4622; Kieffer, B., Befort, K., Gaveriaux-Ruff, C. and Hirth, C.G. (1992). The
δ-opioid receptor: Isolation of a cDNA by expression cloning and pharmacological characterization. Proc. natl. Acad. Sci. USA 89, 12048-12052). This strategy was chosen for its extreme sensitivity since it allows detection of a single "receptor positive" cell by direct microscopic autoradiography. Since the "atypical" receptor has only been described in feeding behavior studies involving injection of NPY and NPY related ligands in rat hypothalamus (see introduction), applicants first examined its binding profile by running competitive displacement studies of ^{125}I-PYY and ^{125}I-PYY$_{3-36}$ on membranes prepared from rat hypothalamus. The competitive displacement data indicate: 1) Human PP is able to displace 20% of the bound ^{125}I-PYY with an IC_{50} of 11 nM (Fig. 1 and Table 2). As can be seen in table 5, this value does not fit with the isolated rat Y1, Y2 and Y4 clones and could therefore correspond to another NPY/PYY receptor subtype. 2) [Leu$_{31}$, Pro$_{34}$] NPY (a Y1 specific ligand) is able to displace with high affinity (IC_{50} of 0.38) 27% of the bound ^{125}I-PYY$_{3-36}$ ligand (a Y2 specific ligand) (Fig. 2 and table 2). These data provide the first evidence based on a binding assay that rat hypothalamic membranes could carry an NPY receptor subtype with a mixed Y1/Y2 pharmacology (referred to as the "atypical" subtype) which fits with the pharmacology defined in feeding behavior studies.

TABLE 2: Pharmacological profile of the rat hypothalamus.

Binding data reflect competitive displacement of ^{125}I-PYY and ^{125}I-PYY$_{3-36}$ from rat hypothalamic membranes. Peptides were tested at concentrations ranging from 0.001 nM to 100 nM unless noted. The IC_{50} value corresponding to 50% displacement, and the

percentage of displacement relative to that produced by 300 nM human NPY, were determined by nonlinear regression analysis. Data shown are representative of at least two independent experiments.

TABLE 2

Peptide	IC_{50} Values, nM (% NPY-produced displacement)	
	^{125}I-PYY	^{125}I-PYY$_{3-36}$
human NPY	0.82 (100%)	1.5 (100%)
human NPY$_{2-36}$	2.3 (100%)	1.2 (100%)
human [Leu^{31},Pro^{34}]NPY	0.21 (44%) 340 (56%)	0.38 (27%) 250 (73%)
human PYY	1.3 (100%)	0.29 (100%)
human PP	11 (20%)	untested

Based on the above data, a rat hypothalamic cDNA library of 3 x 10^6 independent recombinants with a 2.7 kb average insert size was fractionated into 450 pools of »7500 independent clones. All pools were tested in a binding assay with ^{125}I-PYY as described (Y2 patent). Seven pools gave rise to positive cells in the screening assay (# 81, 92, 147, 246, 254, 290, 312). Since Y1, Y2, Y4 and Y5 receptor subtypes (by PCR or binding analysis) are expressed in rat hypothalamus, applicants analyzed the DNA of positive pools by PCR with rat Y1, Y2 and Y4 specific primers. Pools # 147, 246, 254 and 312 turned out to contain cDNAs encoding a Y1 receptor, pool # 290 turned out to encode a Y2 subtype, but pools # 81 and 92 were negative by PCR analysis for Y1, Y2 and Y4 and therefore likely contained a cDNA encoding a new rat hypothalamic NPY receptor (Y5). Pools # 81 and 92 later turned out to contain an identical NPY receptor cDNA. Pool 92 was subjected to sib selection as described until a single clone was isolated (designated CG-18).

The isolated clone carries a 2.8 kb cDNA. This cDNA contains an open reading frame between nucleotides 779 and 2146 that encodes a 456 amino acid protein. The long 5' untranslated region could be involved in the regulation of translation efficiency or mRNA stability. The flanking sequence around the putative initiation codon does not conform to the Kozak consensus sequence for optimal translation initiation (Kozak, M. (1989). The scanning model for translation: an update. J. Cell Biol. 108, 229-241; Kozak, M. (1991). Structural features in eukaryotic mRNAs that modulate the initiation of translation. J. Biol. Chem. 266, 19867-19870). The hydrophobicity plot displayed seven hydrophobic, putative membrane spanning regions which makes the rat hypothalamic Y5 receptor a member of the G-protein coupled superfamily. The nucleotide and deduced amino acid sequences are shown in SEQ ID NOS: 1 and 2, respectively.

Localization studies show that the Y5 mRNA is present in several areas of the rat hippocampus. Assuming a comparable localization in human brain, applicants screened a human hippocampal cDNA library with rat oligonucleotide primers which were shown to yield a DNA band of the expected size in a PCR reaction run on human hippocampal cDNA. Using this PCR screening strategy (Gerald et al, 1994, submitted for publication), three positive pools were identified. One of these pools was analyzed further, and an isolated clone was purified by sib selection. The isolated clone (CG-19) turned out to contain a full length cDNA cloned in the correct orientation for functional expression (see below). The human Y5 nucleotide and deduced amino acid sequences are shown in SEQ ID NOS 3 and 4, respectively. When compared to the rat Y5 receptor the human sequence shows 84.1% nucleotide identity and 87.2% amino acid identity. The rat protein sequence is one amino acid longer at the very end of both amino and carboxy tails of the receptor when compared to the rat. Both pharmacological profiles and functional characteristics of the rat and human Y5 receptor subtype homologs may be expected to match closely.

When the human and rat Y5 receptor sequences were compared to other NPY receptor subtypes or to other human G protein-coupled receptor subtypes, both overall and transmembrane domain identities are very low, showing that the Y5 receptor genes are not closely related to any other previously characterized cDNAs.

The compounds according to the present invention and their pharmaceutically acceptable salts have proven to exhibit pronounced and selective affinity to the Y5 receptor subtype

(shown in Y5 binding test) and in vitro and in vivo antagonistic properties. These properties are shown in vitro by their ability to inhibit NPY-induced calcium increase in stable transfected cells expressing the Y5 receptor and in vivo by their ability to inhibit food intake induced by intracerebroventricular application of NPY or 24 h food deprivation in conscious rats.

Binding experiments

The selective affinity of the compounds according to the present invention to the Y5 receptor is detected in a Y5 binding assay using LM(tk-)-h-NPY5-7 cells which stably express the human NPY Y5 receptor or HEK-293 cells stably expressing the rat NPY Y5 receptor.

The following buffers are used for the preparation of membranes and for binding assay:

a) buffer 1 (homogenisation buffer, pH 7.7 at 4°C) contains Tris-HCl [FLUKA, Buchs, Switzerland] (20 mM) and ethylenediamine tetraacetate (EDTA) [FLUKA, Buchs, Switzerland] (5 mM); b) buffer 2 (suspension buffer, pH: 7.4 at room temperature) contains N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) [Boehringer Mannheim, Germany] (20 mM), NaCl (10 mM), $CaCl_2$ (1.26 mM), $MgSO_4$ (0.81 mM) and KH_2PO_4 (0.22 mM); buffer 3 (binding buffer, pH 7.4 at room temperature) contains HEPES (20 mM), NaCl (10 mM), $CaCl_2$ (1.26 mM), $MgSO_4$ (0.81 mM), KH_2PO_4 (0.22 mM) and 1 mg/ml bovine serum albumin [FLUKA].

Cells are washed in phosphate buffered saline and harvested using a rubber policeman. The cells are homogenised using a Polytron homogeniser (3 bursts of 8 seconds) in ice-cold hypotonic buffer (buffer 1, pH 7.7 at 4°C). The homogenate is centrifuged at 32,000 x g for 20 min at 4°C. The pellets are resuspended in the same buffer and recentrifuged. The final pellets are suspended in buffer 2. Protein concentration is measured by the method of Bradford using the Pierce reagent [PIERCE, Rockford, USA], with bovine serum albumin as standard. The crude membrane preparation is aliquoted, flash-frozen in liquid nitrogen and stored at -80°C. Before use, 0.1% (1 mg/ml) bovine serum albumin is added.

^{125}I-[Pro^{34}]hPYY (60 pM, Anawa, Wangen, Switzerland) dissolved in buffer 3 is used as radioligand. All test compounds are dissolved in dimethyl sulfoxide (DMSO) at 10^{-2} M and diluted to 10^{-3} M in buffer 3. Subsequent dilutions are in buffer 3 plus 10% DMSO. Incubations are performed in Millipore Multiscreen FC filter plates [Millipore, Bedford, USA]. The filters in each well are pretreated with 2% polyethyleneimine for 30 min and rinsed once with 300 microL buffer 3 before use. The following are pipetted into each well: 20 microL

buffer 3, 25 microL ^{125}I-[Pro^{34}]hPYY [SAXON, Hannover, Germany] (600 pM); 25 microL test compound (or binding buffer for the controls); 180 microL crude membrane suspension (approximately 5 microg protein). Incubations are performed at room temperature for 2h. Non-specific binding is defined as the binding remaining in the presence of 1 microM [Pro^{34}]hPYY. The incubations are terminated by rapid filtration and washing four times with 300microL phosphate buffered saline. The filters are removed from the wells, placed into plastic tubes and assayed for radioactivity in a gamma counter [Gammamaster, WALLAC, Finland].

The IC50 values of the compounds according to this invention at the human Y5 receptor range especially between about 0.1 nM and about 10 microM. Representatives are, for example, the final products of working examples 30, 71 and 128, for which following IC50 values [μM/L] were determined: 0.01 (Ex. 30); 0.049 (Ex. 71); 0.05 (Ex. 128).

Measurements of calcium transient

For the determination of in vitro antagonistic properties of the compounds according to the present invention, stably transfected LM(tk-)-hY5-7 cells are used in which a NPY-induced calcium transient is measured as described below. Cells are harvested in a medium containing EDTA (0.5 mM) and phosphate buffered saline (PBS). Cells are then washed in phosphate buffered saline solution and loaded for 90 min at room temperature and pH 7.4 with 10 microM FLUO-AM (fluoro-3-acetoxy methylester, supplemented with pluronic acid as suggested by the manufacturer, Molecular Probes Inc., Eugene, Oregon, USA) in a cell culture buffer of the following composition (NaCl 120 mM, $MgCl_2$ 1 mM, KCl 5.4 mM, NaH_4PO_4 0.33 mM, glucose 11 mM, taurine 5 mM, pyruvate 2 mM, glutamine 1.5 mM HEPES 10 mM, insulin 10 U/l, BSA 0.1% at for 90 min at room temperature. After centrifugation the cells are resuspended in the cell culture buffer at a concentration of 3-4 million cells/ml and supplemented with 200 microM sulfinpyrazone.

Calcium transients are measured at room temperature in a millititer plate using a Cytofluor 2350 (Millipore) with wavelength settings at 485 nm for excitation and 530 nm for emission. 180 microL of cells suspension are preincubated in the presence of various amounts of compounds dissolved in 2 microL DMSO in triplicates (or 2 microL DMSO for the controls) for 5 min and then NPY is added at a final concentration of 100 nM. The compound concentrations giving 50% inhibition of the maximum of the Ca transients are then calculated.

In this cell system, NPY induces Ca transients with an EC50 of 50 nM. The data are analyzed using a Microsoft Excel software. The concentrations which cause a 50% inhibition of the initial control values are given as IC50 values. The IC50 values are determined for the compounds according to the present invention and their pharmaceutically acceptable salts.

The property of the compounds according to the present invention and their pharmaceutically acceptable salts to inhibit NPY-induced increase intracellular calcium indicates their antagonistic properties with IC50 values ranging especially between about 0.1 nM and about 10 microM.

Measurements of NPY-induced food intake in conscious rats

In addition this antagonistic property of the Y5 receptor subtype is also observed in-vivo in conscious rats by their ability to inhibit NPY-induced food intake. For these determinations food intake is measured in normal satiated rats after intracerebroventricular application (i.c.v.) of neuropeptide Y [BACHEM, Feinchemikalien, Bubendorf, Switzerland] in the presence or absence of the compounds according to the present invention. Male Sprague-Dawley rats weighing 180-220 g are used for all experiments. They are individually housed in stainless steel cages and maintained on a 11:13 h light-dark schedule (lights off at 1800 h) under controlled temperature (21-23 °C) at all times. Water and food (NAFAG lab chow pellets) [NAFAG, Gossau, Switzerland] are available ad libitum.

Under pentobarbital [VETERINARIA AB, Zürich, Switzerland] anesthesia, all rats are implanted with a stainless steel guide cannula targeted at the right lateral ventricle. Stereotaxic coordinates, with the incisor bar set -2.0 mm below interaural line, are : -0.8 mm anterior and +1.3 mm lateral to bregma. The guide cannula is placed on the dura. Injection cannulas extended the guide cannulas -3.8 mm ventrally to the skull surface. Animals are allowed at least 4 days of recovery postoperatively before being used in the experiments.

Cannula placement is checked postoperatively by testing all rats for their drinking response to a 50 ng intracerebroventricular (icv) injection of angiotensin II . Only rats which drink at least 2.5 ml of water within 30 min after angiotensin II injection are used in the feeding studies. Injections are made in the morning 2 hours after light onset. Peptides are injected in artificial cerebrospinal fluid (ACSF) [FLUKA, Buchs, Switzerland] in a volume of 5 μl. The ACSF contains NaCl 124 mM, KCl 3.75 mM, $CaCl_2$ 2.5 mM, $MgSO_4$ 2.0 mM, KH_4PO_4 0.22 mM, $NaHCO_3$ 26 mM and glucose 10 mM. NPY (300 pmole) is administered by the

intracerebroventricular route 10-60 minutes after administration of compounds or vehicle DMSO/water (10%,v/v) or cremophor/water (20%,v/v) [SIGMA, Buchs, Switzerland].

Food intake is measured by placing preweighed pellets into the cages at the time of NPY injection. Pellets are removed from the cage subsequently at each time point indicated in the figures and replaced with a new set of preweighed pellets.
All results are presented as means ±SEM. Statistical analysis is performed by analysis of variance using Student-Newman-Keuls test.

The compounds according to the present invention inhibit NPY-induced food intake in rats in a range especially of about 0.01 to about 100 mg/kg after oral, intraperitoneal, subcutaneous or intravenous administration.

Measurements of food intake in 24 hours food deprived rats

Based on the observation that food deprivation induces an increase in the hypothalamic NPY levels, it is assumed that NPY mediates food intake induced by food deprivation. Thus, the compounds according to the present invention are also tested in rats after 24 hours food deprivation. These experiments are conducted with male Sprague-Dawley (CIBA-GEIGY AG, Sisseln, Switzerland] rats weighing between 220 and 250 g. The animals are housed in individual cages for the duration of the study and allowed free access to normal food together with tap water. The animals are maintained in room with a 12 h light/dark cycle (8 a.m. to 8.00 p.m. light) at 24°C and monitored humidity. After placement into the individual cages the rats undergo a 2-4 days equilibration period, during which they are habituated to their new environment and to eating a powdered or pellet diet [NAFAG, Gossau, Switzerland]. At the end of the equilibration period, food is removed from the animals for 24 hours starting at 8.00 a.m. At the end of the fasting period the animals are injected intraperitoneally, intravenously or orally either with the compounds according to the present invention or an equivalent volume of vehicle DMSO/water (10%, v/v) or cremophor/water (20%, v/v) and 10-60 min later the food is returned to them. Food intake at various time periods is monitored over the following 24 hour period. Inhibition of food intake by the compounds according to the present invention is given in percentage of the respective control vehicle-treated rats.
The compounds according to the present invention inhibit food intake in this food deprived rat model in a range especially of about 0.01 to about 100 mg/kg after oral, intraperitoneal, subcutaneous or intravenous administration. Representative is, for example, the final

product of working example 128, for which an inhibition of food intake of 62% versus the respective control vehicle-treated animals after i.p. application of 30 mg/kg was determined.

Measurements of food intake in obese Zucker rats

The antiobesity efficacy of the compounds according to the present invention can also be shown in Zucker obese rats, an art-known animal model of obesity. These studies are conducted with male Zucker fatty rats (fa/fa) [HARLAN CPB, Austerlitz, NL] weighing between 480 and 500 g. Animals are individually housed in metabolism cages for the duration of the study and allowed free access to powdered food together with tap water. The animals are maintained in a room with a 12 hour light/dark cycle (8 a.m. to 8.00 p.m. light) at 24°C and monitored humidity. After placement into the metabolism cages the rats undergo a 6 day equilibration period, during which they are habituated to their new environment and to eating a powdered diet. At the end of the equilibration period, food intake during the light and dark phases is determined. After a 3 day control period, the animals are treated with the compounds according to the present invention or vehicle DMSO/water (10%, v/v) or cremophor/water (20%, v/v).

The compounds according to the present invention inhibit food intake in Zucker obese rats in a range especially of about 0.01 to about 100 mg/kg after oral, intraperitoneal, subcutaneous or intravenous administration.

The above experiments clearly demonstrate that the Y5 receptor subtype is the primary mediator of NPY-induced feeding and that corresponding antagonists can be used for the treatment of obesity and related disorders [*Nature, Vol. 382, 168-171 (1996)*].

The compounds according to the present invention can inhibit food intake induced either by intracerebroventricular application of NPY or by food deprivation or as well as spontaneous eating in the Zucker obese rat. Thus, the compounds according to the present invention can especially be used for the treatment and prophylaxis of disorders or diseases associated with the Y5 receptor subtype, especially in the treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyspilipidimia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain and additionally in the treatment of sexual/reproductive

disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The compounds according to the present invention act as antagonists of neuropeptide Y (NPY) binding at the Y5 receptor subtype. By virtue of their Y5 receptor antagonistic property, the compounds of the formula (I) and their pharmaceutically acceptable salts can therefore be used, for example, as pharmaceutical active ingredients in pharmaceutical compositions which are employed, for example, for the prophylaxis and treatment of diseases and disorders associated with NPY Y5 receptor subtype, especially in the treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyspilipidimia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The invention relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as described hereinbefore and hereinafter for the manufacture of a pharmaceutical composition for the prophylaxis and treatment of diseases or disorders associated with NPY Y5 receptor subtype, especially in the treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyspilipidimia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The invention relates to a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as described hereinbefore and hereinafter for the prophylaxis and treatment of diseases or disorders associated with NPY Y5 receptor subtype, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyspilipidimia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and

additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R_2 represents

(i) hydrogen, halogen, nitro, cyano, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by lower alkoxy, by substituted amino, by lower alkoxycarbonyl, or by N-substituted carbamoyl;

(ii) substituted amino;

(iii) hydroxy, lower alkoxy, lower alkoxy-lower alkoxy, C_3-C_8-cyclo-alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-O-R, -NR_1-CO-R, -NR_1-CO-NR_1-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X_1(X_2)(X_3) wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula -X_4-$(CO)_p$-$(CH_2)_o$-, -$(CH_2)_q$-X_4-$(CO)_p$-$(CH_2)_r$-, or -$(CH_2)_s$-X_4-CO-$(CH_2)_t$-; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula -CO-$(CH_2)_u$-; [X_4 being -CH_2-, -N(R_1)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from -CH_2-;];

R_3 and R_4 , independently of one another, represent
(i) hydrogen, lower alkyl, lower alkenyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, N-substituted carbamoyl, and -$S(O)_n$-R;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, or NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents phenylene, naphthylene, thiophenylene, furylene, or pyridylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of
(i) halogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iv) amino, substituted amino;
(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived and selected from the group consisting of phenyl, biphenylyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl,

pyridyl, indolyl, indazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinolinyl, isoquinolinyl, or quinazolinyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, or lower alkoxy-lower alkyl;

R_2 represents

(i) hydrogen, halogen, nitro, cyano, lower alkyl, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryl, or lower alkyl which is substituted by halogen, by lower alkoxy, by substituted amino, by lower alkoxycarbonyl, or by substituted carbamoyl;

(ii) substituted amino;

(iii) lower alkoxy, lower alkoxy-lower alkoxy, C_3-C_8-cyclo-alkoxy, or (carbocyclic or heterocyclic) aryl-lower alkoxy,;

(iv) hydroxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined

above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X_1(X_2)(X_3) wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula -X_4-$(CO)_p$-$(CH_2)_o$-, -$(CH_2)_q$-X_4-$(CO)_p$-$(CH_2)_r$-, or -$(CH_2)_s$-X_4-CO-$(CH_2)_t$-; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula -CO-$(CH_2)_u$-; [X_4 being -CH_2-, -N(R_1)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from -CH_2-;];

R_3 and R_4 , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: lower alkoxy, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, and substituted carbamoyl;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, or NR_0];

X represents phenylene, naphthylene, thiophenylene, furylene, or pyridylene which, in each case, is unsubstituted or substituted by halogen, cyano, lower alkyl, halo-lower alkyl, lower alkoxy, lower alkanoyloxy, or lower alkanoyl;

wherein, in each case, if not indicated otherwise, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy,

amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) substituted amino;

(v) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, is derived from phenyl, naphthyl or pyridyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 represents a single bond or C_1-C_3-alkylene;

alk_2 represents a single bond or C_1-C_3-alkylene;

R_1 represents hydrogen, lower alkyl or lower alkyl which is substituted by lower alkoxy-carbonyl;

R_2 represents

(i) hydrogen, halogen, cyano, nitro, lower alkyl, C_3-C_7-cycloalkyl, or phenyl;

(ii) amino, amino which is mono-substituted by lower alkyl, by lower alkoxy-lower alkyl, by phenyl, by pyridyl, or which is disubstituted by lower alkyl or by C_2-C_6-alkylene;
(iii) hydroxy, lower alkanoyloxy, or lower alkoxy which is unsubstituted or substituted by hydroxy, by lower alkoxy, by phenyl-lower alkoxy, by lower-alkanoyloxy, by C_3-C_8-cycloalkyl or by phenyl;
(iv) a group selected from -NR_1-CO-R, -NR_1-SO_2-R, -SO_2-R, or -SO_2-NR_1-R, [R being lower alkyl, lower alkoxy-lower alkyl, phenyl, or naphthyl, and the group -N(R)(R_1) represents amino which is mono-substituted by lower alkyl or by lower alkoxy-lower alkyl, or which is di-substituted by lower alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or lower alkyl}];
(vi) carbamoyl;

R_3 represents hydrogen, lower alkyl which is unsubstituted or substituted by C_3-C_7-cycloalkyl, by phenyl, or by di-lower alkylamino, or represents C_3-C_7-cycloalkyl, phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, hydroxy, and carbamoyl, or represents indazolyl;

R_4 represents hydrogen or lower alkyl which is unsubstituted or substituted by lower alkoxy-carbonyl; or

R_3 and R_4 together represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, halo-lower alkyl, lower alkoxy, or oxy-lower alkylene-oxy, or represents nahthylene;

wherein the benzo ring A is unsubstituted or substituted a substituent selected from the group consisting of: halogen, nitro, amino, di-lower alkylamino, lower alkyl, lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower alkyl, di-(lower alkyl)-amino-lower alkyl, phenyl, and lower alkanoyl.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 represents a single bond;

alk_2 represents a single bond or C_1-C_3-alkylene;

R_1 represents hydrogen or lower alkyl;

R_2 represents

(i) hydrogen, halogen, cyano, nitro, lower alkyl, or phenyl;

(ii) amino which is mono-substituted by lower alkyl, phenyl or pyridyl, or which is disubstituted by lower alkyl or by C_2-C_6-alkylene;

(iii) hydroxy or lower alkoxy which is unsubstituted or substituted by C_3-C_8-cycloalkyl or by phenyl;

(iv) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, or -SO_2-NR_1-R, [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl, R_1 being as defined above, or the group -N(R)(R_1) represents amino which is mono-substituted by lower alkyl, by hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or lower alkyl}];

R_3 represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R_4 represents hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, halo-lower alkyl, lower alkoxy, lower alkoxy-lower alkyl;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

halogen, lower alkyl, halo-lower alkyl, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

(a) alk_1 and alk_2 both represents a single bond; and

R_2 represents (i) hydrogen, halogen, cyano, nitro, lower alkyl, or phenyl;

(ii) amino which is mono-substituted by lower alkyl, phenyl or pyridyl, or which is disubstituted by lower alkyl or by C_2-C_6-alkylene;

(iii) hydroxy or lower alkoxy which is unsubstituted or substituted by C_3-C_8-cycloalkyl, or by phenyl; or

(b) alk_1 represents a single bond; and

alk_2 represents a single bond or C_1-C_3-alkylene; and, in each case,

R_2 represents (iv) a group selected from -NR_1-CO-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, or -SO_2-NR_1-R, [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl, R_1 being as defined below, or the group -N(R)(R_1) represents amino which is mono-substituted by lower alkyl, by hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or lower alkyl}];

R_1 represents hydrogen or lower alkyl;

R_3 represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R_4 represents hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, or lower alkoxy;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of
halogen, lower alkyl, halo-lower alkyl, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

(a) alk_1 and alk_2 both represents a single bond; and

R_2 represents hydrogen, amino which is disubstituted by by C_2-C_6-alkylene, especially pentylene, or C_1-C_4-alkoxy, especially methoxy; or

(b) alk_1 represents a single bond; alk_2 represents C_1-C_3-alkylene; and

R_2 represents (iv) a group selected from -NH-SO_2-R , -SO_2-R, or -SO_2-NH-R, [R being C_1-C_4-alkyl, or naphthyl, or the group -NH(R) represents amino which is mono-substituted by C_1-C_4-alkyl, by hydroxy-C_1-C_4-alkyl, or by naphthyl, or which is di-substituted by C_1-C_4-alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or C_1-C_4-alkyl}];

and, in each case,

R_1 represents hydrogen;

R_3 represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, C_1-C_4-alkyl, C_1-C_4-alkoxy, and oxy- C_1-C_4-alkylene-oxy; and

R_4 represents hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, C_1-C_4-alkyl, or C_1-C_4-alkoxy;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 represents a single bond;

alk_2 represents a single bond or C_1- or C_2-alkylene;

R_1 represents hydrogen;

R_2 represents hydrogen, hydroxy, C_1-C_4-alkoxy, especially methoxy, lower alkoxy-lower alkoxy, phenyl-lower alkoxy-lower alkoxy, amino, amino which is disubstituted by by C_2-C_6-alkylene, especially pentylene, lower alkoxycarbonyl-amino, or -SO_2-R or -SO_2-NH-R and R being C_1-C_4-alkyl, especially methyl; and, in each case;

R_3 represents C_3-C_6-cycloalkyl, phenyl-lower alkyl, or phenyl which is unsubstituted or is substituted by halogen, hydroxy, or lower alkoxy;

R_4 represents hydrogen; and

X represents 1,4-phenylene or 1,3-phenylene which is di-substituted by oxy-methylene-oxy;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

(a) alk_1 and alk_2 both represent a single bond; and R_2 represents hydrogen, C_1-C_4-alkoxy, espcially methoxy, or amino which is disubstituted by by C_2-C_6-alkylene, especially pentylene; or

(b) alk_1 represents a single bond; and alk_2 represents C_1- or C_2-alkylene; and R_2 represents -SO_2-R or -SO_2-NH-R and R being C_1-C_4-alkyl, especially methyl; and, in each case,

R_1 represents hydrogen;

R_3 represents phenyl which is unsubstituted or is substituted by lower alkoxy;

R_4 represents hydrogen; and

X represents 1,4-phenylene;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

The invention most preferably relates to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which
(a) alk_1 and alk_2 both represent a single bond; and R_2 is hydrogen, 1-piperidino or C_1-C_4-alkoxy, especially methoxy; the benzo ring A is unsubstituted or substituted in position 8 of the quinazoline ring by C_1-C_4-alkoxy, especially methoxy, or
(b) alk_1 is a single bond and alk_2 represents methylene; and R_2 is -SO_2-NH-R and R is C_1-C_4-alkyl, especially methyl; the benzo ring A is unsubstituted; and, in each case,
R_1 is hydrogen; R_3 is phenyl; R_4 is hydrogen; X is 1,4-phenylene.

The invention most preferably relates to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2 both represent a single bond;

R_1 is hydrogen;

R_4 is hydrogen;

X is 1,4-phenylene;

R_2 is C_1-C_4-alkoxy, especially methoxy, and R_3 is phenyl which is substituted by hydroxy, especially 3-hydroxy-phenyl; or

R_2 is C_1-C_4-alkoxy-C_1-C_4-alkoxy, especially 2-methoxy-ethoxy, or 1-piperidino; and

R_3 is phenyl; and

the benzo ring A is unsubstituted or substituted in position 8 of the quinazoline ring by C_1-C_4-alkoxy, especially methoxy.

The invention likewise relates to a new compound of formula (I) or a salt thereof as described hereinbefore or hereinafter.

The invention relates especially to a new compound of formula (I) or a salt thereof, for example, in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R_2 represents a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-O-R, -NR_1-CO-R, -NR_1-CO-NR_1-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X_1(X_2)(X_3) wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula -X_4-$(CO)_p$-$(CH_2)_o$-, -$(CH_2)_q$-X_4-$(CO)_p$-$(CH_2)_r$-, or -$(CH_2)_s$-X_4-CO-$(CH_2)_t$-; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula -CO-$(CH_2)_u$-; [X_4 being -CH_2-, -N(R_1)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from -CH_2-;];

R_3 and R_4 , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, N-substituted carbamoyl, and -$S(O)_n$-R;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents (carbocyclic or heterocyclic) arylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, lower alkynyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, (carbocyclic or heterocyclic) aroyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by $-CO-(O)_v-R$ and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen, lower alkyl, lower alkenyl, lower alkinyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, $-SO_2-R$, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy;

wherein, in each case, R represents hydrogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R_2 represents

(vi) a group selected from $-CH(OH)-R$, $-CO-R$, $-NR_1-CO-O-R$, $-NR_1-CO-R$, $-NR_1-CO-NR_1-R$, $-NR_1-SO_2-R$, $-NR_1-SO_2-NR_1-R$, $-SO_2-R$, $-SO_2-NR_1-R$, or $-SO_2-NR_1-CO-R$, [R being as defined below and R_1 being as defined above, or the group $-N(R)(R_1)$ represents amino which is di-substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula $-X_1(X_2)(X_3)$ wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula $-X_4-(CO)_p-(CH_2)_o-$, $-(CH_2)_q-X_4-(CO)_p-(CH_2)_r-$, or $-(CH_2)_s-X_4-CO-(CH_2)_t-$; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula $-CO-(CH_2)_u-$; [X_4 being $-CH_2-$, $-N(R_1)-$ or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from $-CH_2-$;];

R_3 and R_4 , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, N-substituted carbamoyl, and $-S(O)_n-R$;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, or NR_6] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents phenylene, naphthylene, thiophenylene, furylene, or pyridylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived and selected from the group consisting of phenyl, biphenylyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl, pyridyl, indolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinolinyl, isoquinolinyl, or quinazolinyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O,

$S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, or lower alkoxy-lower alkyl;

R_2 represents

(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X_1(X_2)(X_3) wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula -X_4-$(CO)_p$-$(CH_2)_o$-, -$(CH_2)_q$-X_4-$(CO)_p$-$(CH_2)_r$-, or -$(CH_2)_s$-X_4-CO-$(CH_2)_t$-; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula -CO-$(CH_2)_u$-; [X_4 being -CH_2-, -N(R_1)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from -CH_2-;];

R_3 and R_4 , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: lower alkoxy, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, and substituted carbamoyl;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, or NR_0];

X represents phenylene, naphthylene, thiophenylene, furylene, or pyridylene which, in each case, is unsubstituted or substituted by halogen, lower alkyl, halo-lower alkyl, lower alkoxy, lower alkanoyloxy, or lower alkanoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of
(i) halogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iv) substituted amino;
(v) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl represents (phenyl-, naphthyl- or pyridyl)-lower alkoxy-carbonyl;

wherein, in each case, (carbocyclic or heterocyclic) aryl-lower alkyl represents phenyl-, naphthyl- or pyridyl-lower alkyl;

wherein, in each case, (carbocyclic or heterocyclic) aryl-oxy represents phenoxy, naphthyloxy, or pyridyloxy;

wherein, in each case, (carbocyclic or heterocyclic) aryl-lower alkanoyl represents (phenyl-, naphthyl- or pyridyl)-lower alkanoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-

cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by $-CO-(O)_v-R$ and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk_1 represents a single bond or C_1-C_3-alkylene;

alk_2 represents a single bond or C_1-C_3-alkylene;

R_1 represents hydrogen, lower alkyl or lower alkyl which is substituted by lower alkoxy-carbonyl;

R_2 represents a group selected from $-NR_1-CO-R$, $-NR_1-SO_2-R$, $-SO_2-R$, or $-SO_2-NR_1-R$, [R being lower alkyl, lower alkoxy-lower alkyl, phenyl, or naphthyl, and the group $-N(R)(R_1)$ represents amino which is mono-substituted by lower alkyl or by lower alkoxy-lower alkyl, or which is di-substituted by lower alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or lower alkyl}];

(vi) carbamoyl;

R_3 represents hydrogen, lower alkyl which is unsubstituted or substituted by C_3-C_7-cycloalkyl, by phenyl, or by di-lower alkylamino, or represents C_3-C_7-cycloalkyl, phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, hydroxy, and carbamoyl, or represents indazolyl;

R_4 represents hydrogen or lower alkyl which is unsubstituted or substituted by lower alkoxy-carbonyl; or

R_3 and R_4 together represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, halo-lower alkyl, lower alkoxy, or oxy-lower alkylene-oxy, or represents nahthylene;

wherein the benzo ring A is unsubstituted or substituted a substituent selected from the group consisting of: halogen, nitro, amino, di-lower alkylamino, lower alkyl, lower alkoxy,

lower alkoxy-lower alkoxy, lower alkoxy-lower alkyl, di-(lower alkyl)-amino-lower alkyl, phenyl, and lower alkanoyl.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk_1 represents a single bond;

alk_2 represents a single bond or C_1-C_3-alkylene;

R_1 represents hydrogen or lower alkyl;

R_2 represents

(iv) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, or -SO_2-NR_1-R, [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl, R_1 being as defined above, or the group -N(R)(R_1) represents amino which is mono-substituted by lower alkyl, by hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or lower alkyl}];

R_3 represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R_4 represents (i) hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, halo-lower alkyl, or lower alkoxy;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

halogen, lower alkyl, halo-lower alkyl, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk_1 represents a single bond;

alk_2 represents a single bond or C_1-C_3-alkylene;

R_1 represents hydrogen or lower alkyl;

R_2 represents

(iv) a group selected from -NR_1-CO-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, or -SO_2-NR_1-R, [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl, R_1 being as defined below, or the group -N(R)(R_1) represents amino which is mono-substituted by lower alkyl, by

hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or lower alkyl}];

R_3 represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R_4 represents (i) hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, or lower alkoxy;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of
halogen, lower alkyl, halo-lower alkoxy, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk_1 represents a single bond;

alk_2 represents a single bond or C_1-C_3-alkylene;

R_1 represents hydrogen or lower alkyl;

R_2 represents
(iv) a group selected from -NR_1-CO-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, or -SO_2-NR_1-R, [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl, R_1 being as defined above, or the group -N(R)(R_1) represents amino which is mono-substituted by lower alkyl, by hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or lower alkyl}];

R_3 represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R_4 represents (i) hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, or lower alkoxy;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of
halogen, lower alkyl, halo-lower alkoxy, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk_1 represents a single bond;

alk_2 represents a single bond or C_1- or C_2-alkylene;

R_1 represents hydrogen;

R_2 represents $-SO_2-R$ or $-SO_2-NH-R$ and R being C_1-C_4-alkyl, especially methyl; and, in each case;

R_3 represents C_3-C_6-cycloalkyl, phenyl-lower alkyl, or phenyl which is unsubstituted or is substituted by halogen, hydroxy, or lower alkoxy;

R_4 represents hydrogen; and

X represents 1,4-phenylene or 1,3-phenylene which is di-substituted by oxy-methylene-oxy;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk_1 and alk_2 both represent a single bond;

R_1 is hydrogen;

R_4 is hydrogen;

X is 1,4-phenylene;

R_2 is C_1-C_4-alkoxy, especially methoxy, and R_3 is phenyl which is substituted by hydroxy, especially 3-hydroxy-phenyl; or

R_2 is C_1-C_4-alkoxy-C_1-C_4-alkoxy, especially 2-methoxy-ethoxy, or 1-piperidino; and

R_3 is phenyl; and

the benzo ring A is unsubstituted or substituted in position 8 of the quinazoline ring by C_1-C_4-alkoxy, especially methoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk_1 represents a single bond;

alk_2 represents C_1-C_3-alkylene; and

R_2 represents (iv) a group selected from $-NH-SO_2-R$, $-SO_2-R$, or $-SO_2-NH-R$, [R being C_1-C_4-alkyl, or naphthyl, or the group -NH(R) represents amino which is mono-substituted by C_1-C_4-alkyl, by hydroxy-C_1-C_4-alkyl, or by naphthyl, or which is di-substituted by C_1-C_4-alkyl

or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or C_1-C_4-alkyl}];

R_1 represents hydrogen;

R_3 represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, C_1-C_4-alkyl, C_1-C_4-alkoxy, and oxy- C_1-C_4-alkylene-oxy; and

R_4 represents (i) hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, lower alkoxy-lower alkyl;

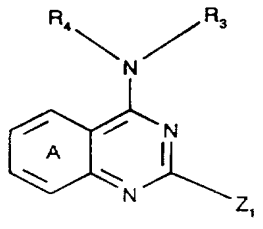
wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which alk_1 is a single bond and alk_2 represents methylene; and R_2 is $-SO_2$-NH-R and R is C_1-C_4-alkyl, especially methyl; the benzo ring A is unsubstituted; and, in each case, R_1 is hydrogen; R_3 is phenyl; R_4 is hydrogen; X is 1,4-phenylene.

The invention relates in particular to the novel compounds shown in the examples and to the modes of preparation described therein.

The invention relates to processes for the preparation of the compounds according to the invention. The preparation of new compounds of the formula (I) and their salts comprises, for example,

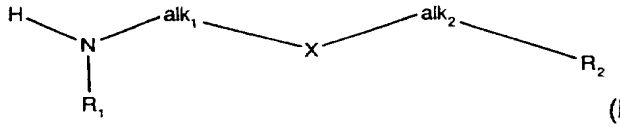
(a) reacting a compound of formula (IIa) or a salt thereof



(IIa)

in which Z_1 represents a leaving group,

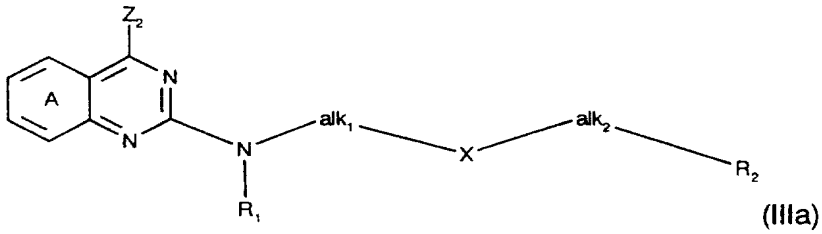
with a compound of formula (IIb) or a salt thereof



(IIb)

or

(b) reacting a compound of formula (IIIa) or a salt thereof



(IIIa)

in which Z_2 is a leaving group

with a compound of formula $HN(R_3)(R_4)$ (IIIb) or a salt thereof,

and, if desired, converting a compound (I) obtainable according to the process or in another manner, in free form or in salt form, into another compound (I), separating a mixture of isomers obtainable according to the process and isolating the desired isomer and/or converting a free compound (I) obtainable according to the process into a salt or converting a salt of a compound (I) obtainable according to the process into the free compound (I) or into another salt.

The reactions described above and below in the variants are carried out in a manner known per se, for example in the absence or, customarily, in the presence of a suitable solvent or diluent or a mixture thereof, the reaction, as required, being carried out with cooling, at room temperature or with warming, for example in a temperature range from about -80°C up to the boiling point of the reaction medium, preferably from about -10° to about +200°C, and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions. The person skilled in the pertinent art is especially referred to the methods as outlined in the working examples based upon which the person skilled in the art is enabled to carry out the manufacture of the compounds of formula (I).

Salts of starting materials which have at least one basic centre, for example of the formula IIIb, are appropriate acid addition salts, while salts of starting materials which have an acidic group, for example of the formula (IIb), are present as salts with bases, in each case as mentioned above in connection with corresponding salts of the formula (I).

A leaving group Z_1 or Z_2, respectively, is, for example, reactive esterified hydroxy, or is R'-S(O)$_p$- [the integer u being 0, 1 or 2 and R' being lower alkyl, halo-lower alkyl or aryl, such as methyl, trifluoromethyl or p-toluyl], or is lower alkoxy. Reactive esterified hydroxyl Z_4 is in particular hydroxyl esterified with a strong inorganic acid or organic sulfonic acid, for example halogen, such as fluorine, chlorine, or bromine, sulfonyloxy, such as hydroxysulfonyloxy, halosulfonyloxy, for example fluorosulfonyloxy, C_1-C_7-alkane-sulfonyloxy which is unsubstituted or substituted, for example by halogen, for example methane- or trifluoromethanesulfonyloxy, C_5-C_7cycloalkanesulfonyloxy, for example cyclohexanesulfonyloxy, or benzenesulfonyloxy which is unsubstituted or substituted, for example by C_1-C_7-alkyl or halogen, for example p-bromobenzene- or p-toluenesulfonyloxy. Preferred Z_1 or Z_2 is chloro, bromo or iodo, methanesulfonyloxy or trifluoromethanesulfonyloxy, or p-toluenesulfonyloxy, or methylthio or methoxy.

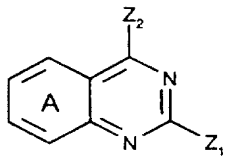
The reactions of process variants (a) and (b) are carried out, if necessary, in the presence of a base. Suitable bases are, for example, alkali metal hydroxides, hydrides, amides, alkanolates, carbonates, triphenylmethylides, di-lower alkylamides, aminoalkylamides or lower alkylsilylamides, naphthaleneamines, lower alkylamines, basic heterocycles, ammonium hydroxides, and carbocyclic amines. Examples which may be mentioned are sodium hydroxide, sodium hydride, sodium amide, sodium methoxide, sodium ethoxide, potassium tert-butoxide, potassium carbonate, lithium triphenylmethylide, lithium diisopropylamide, potassium 3-(aminopropyl)amide, potassium bis(trimethylsilyl)amide, dimethylaminonaphthalene, di- or triethylamine, or ethyldiisopropylamine, N-methylpiperidine, pyridine, benzyltrimethylammonium hydroxide, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU).

The starting material of fomulae (IIa), (IIb), (IIIa), and (IIIb) is essentially known or is accessible analogously to preparation processes known per se.

Starting material of the formula (IIa) is, for example, described, for example, in US Patent No. 5,064,833.

The starting material of formula (IIb) in which R_2 represents N-acylated or N-alkylated amino, such as a group of formula $-NR_1-CO-O-R$, $-NR_1-CO-R$, $-NR_1-CO-NR_1-R$, $-NR_1-SO_2-R$,$-NR_1-SO_2-NR_1-R$, or N-substituted amino, is accessible, for example, by N-acylating or by N-alkylating, respectively, a, preferably N-protected, compound of the formula $NH(R_1)-alk_1-X-alk_2-Z_3$ (IIc) in which Z_3 represents a group which is convertable to R_2, such as amino, carboxy, or hydroxy. Conventional protecting groups may be used, for example, t-butoxycarbonyl which will be split off after the N-acylation or the N-alkylation, respectively. The starting material of formula (IIb) in which R_2 represents carbamoyl or N-substituted carbamoyl, or esterified carboxy, can be manufactured starting from a compound of formula (IIc) in which Z_3 represents carboxy. The esterification or amidation can be carried out in a manner known per se. Starting fom a compound of formula (IIc) in which Z_3 is hydroxy, corresponding etherified or esterified derivatives are accessible using etherification or esterifaction methods known in the art.

The starting material of formula (IIIa) is accessible, for example, by selectively converting the 4-Z_2-group into a group which is desactivated, for example, by selectively hydrolyzing a compound of formula (IIIc)



(IIa)

or a salt thereof to form a corresponding 4-hydroxy-compound which is in the next step reacted with a compound of formula (IIb) to introduce the corresponding side chain into position 2 of the quinazolin ring. Reactivation of the 4-position, for example, by reaction with a halogenating agent, such as $POCl_3$, leads to

corresponding compounds of formula (IIIa).

A compound according to the invention which is obtainable by the process can be converted into another compound according to the invention in a manner known per se.

A compound according to the invention containing hydroxyl can be etherified by methods known per se. The etherification can be carried out, for example, using an alcohol, such as a substituted or unsubstituted lower alkanol, or a reactive ester thereof. Suitable reactive esters of the desired alcohols are, for example, those with strong inorganic or organic acids, such as corresponding halides, sulfates, lower alkanesulfonates or substituted or unsubstituted benzenesulfonates, for example chlorides, bromides, iodides, methane-, benzene- or p-toluenesulfonates. The etherification can be carried out, for example, in the presence of a base, an alkali metal hydride, hydroxide or carbonate, or of an amine. Conversely, corresponding ethers, such as lower alkoxy compounds, can be cleaved, for example, by means of strong acids, such as mineral acids, for example the hydrohalic acids hydrobromic or hydriodic acid, which may advantageously be present in the form of pyridinium halides, or by means of Lewis acids, for example halides of elements of main group III or the corresponding sub-groups. These reactions can be carried out, if necessary, with cooling or warming, for example in a temperature range from about -20° to about 100°C, in the presence or absence of a solvent or diluent, under inert gas and/or under pressure and, if appropriate, in a closed vessel.

Compounds according to the invention containing hydroxymethyl groups can be prepared, for example, starting from compounds containing corresponding carboxyl or esterified carboxyl, corresponding compounds being reduced in a manner known per se, for example by reduction with a hydride which, if desired, may be complex, such as a hydride formed from an element of the 1st and 3rd main groups of the periodic table of the elements, for example borohydride or aluminohydride, for example lithium borohydride, lithium aluminium hydride, diisobutylaluminium hydride (an additional reduction step using alkali metal cyanoborohydride, such as sodium cyanoborohydride, may be necessary), and

also diborane.

If an aromatic structural component is substituted by (lower) alkylthio (in $S(O)_n$ -R n is 0), this can be oxidised in a customary manner to corresponding (lower) alkanesulfinyl or -sulfonyl. Suitable oxidising agents for the oxidation to the sulfoxide step are, for example, inorganic peracids, such as peracids of mineral acids, for example periodic acid or persulfuric acid, organic peracids, such as appropriate percarboxylic or persulfonic acids, for example performic, peracetic, trifluoroperacetic or perbenzoic acid or p-toluenepersulfonic acid, or mixtures of hydrogen peroxide and acids, for example a mixture of hydrogen peroxide with acetic acid.

The oxidation is commonly carried out in the presence of suitable catalysts, catalysts which can be mentioned being suitable acids, such as substituted or unsubstituted carboxylic acids, for example acetic acid or trifluoroacetic acid, or transition metal oxides, such as oxides of elements of sub-group VII, for example vanadium oxide, molybdenum oxide or tungsten oxide. The oxidation is carried out under mild conditions, for example at temperatures from about -50° to about +100°C.

The oxidation to the sulfone step may also be carried out appropriately at low temperatures using dinitrogen tetroxide as the catalyst in the presence of oxygen, just like the direct oxidation of (lower) alkylthio to (lower) alkanesulfonyl. However, in this case the oxidising agent is customarily employed in an excess.

If one of the variables contains amino, corresponding compounds of the formula (I), their tautomers or salts can be N-alkylated in a manner known per se; likewise, carbamoyl or radicals containing carbamoyl can be N-alkylated. The (aryl)alkylation is carried out, for example, using a reactive ester of an (aryl)C_1-C_7alkyl halide, for example a bromide or iodide, (aryl)C_1-C_7alkylsulfonate, for example methanesulfonate or p-toluenesulfonate, or a di-C_1-C_7alkyl sulfate, for example dimethyl sulfate, preferably under basic conditions, such as in the presence of sodium hydroxide solution or potassium hydroxide solution, and advantageously in the presence of a phase transfer catalyst, such as

tetrabutylammonium bromide or benzyltrimethylammonium chloride, where, however, stronger basic condensing agents, such as alkali metal amides, hydrides or alkoxides, for example sodium amide, sodium hydride or sodium ethoxide, may be necessary. Amino can also be acylated in a manner known per se.

In compounds of the formula (I) which contain an esterified or amidated carboxyl group as a substituent, a group of this type can be converted into a free carboxyl group, for example by means of hydrolysis, for example in the presence of a basic agent, or of an acidic agent, such as a mineral acid. tert-Butyloxycarbonyl, for example, can furthermore be converted into carboxyl, for example in a manner known per se, such as treating with trihaloacetic acid, such as trifluoroacetic acid, and benzyloxycarbonyl can be converted into carboxyl, for example by catalytic hydrogenation in the presence of a hydrogenation catalyst, for example in the manner described below.

Furthermore, in compounds of the formula (I) which contain a carboxyl group as a substituent, this can be converted into an esterified carboxyl group, for example, by treating with an alcohol, such as a lower alkanol, in the presence of a suitable esterifying agent, such as an acid reagent, for example an inorganic or organic acid or a Lewis acid, for example zinc chloride, or a condensing agent which binds water, for example a carbodiimide, such as N,N'-dicyclohexylcarbodiimide, or by treating with a diazo reagent, such as with a diazo-lower alkane, for example diazomethane. This can also be obtained if compounds of the formula (I) in which the carboxyl group is present in free form or in salt form, such as ammonium salt or metal salt form, for example alkali metal salt form, such as sodium salt or potassium salt form, are treated with a reactive ester of a (C_1-C_7)alkyl halide, for example methyl or ethyl bromide or iodide, or an organic sulfonic acid ester, such as an appropriate (C_1-C_7)alkyl ester, for example methyl or ethyl methanesulfonate or p-toluenesulfonate.

Compounds of the formula (I) which contain an esterified carboxyl group as a substituent can be transesterified into other ester compounds of the formula (I) by transesterification, for example by treating with an alcohol, customarily a higher

appropriate alcohol than that of the esterified carboxyl group in the starting material, in the presence of a suitable transesterifying agent, such as a basic agent, for example an alkali metal (C_1-C_7)alkanoate, (C_1-C_7)alkanolate or alkali metal cyanide, such as sodium acetate, sodium methoxide, sodium ethoxide, sodium tert-butoxide or sodium cyanide, or a suitable acid agent, if appropriate with removal of the resulting alcohol, for example by distillation. Appropriate, so-called activated esters of the formula (I) which contain an activated esterified carboxyl group as a substituent may also be used as starting materials (see below), and these may be converted into another ester by treating with a (C_1-C_7)alkanol.

In compounds of the formula (I) which contain the carboxyl group as a substituent, this can also first be converted into a reactive derivative, such as an anhydride, including a mixed anhydride, such as an acid halide, for example an acid chloride (for example by treating with a thionyl halide, for example thionyl chloride), or an anhydride using a formic acid ester, for example a (C_1-C_7)alkyl ester (for example by treating a salt, such as an ammonium or alkali metal salt, with a haloformic acid ester, such as a chloroformic acid ester, such as a (C_1-C_7)alkyl ester), or into an activated ester, such as a cyanomethyl ester, a nitrophenyl ester, for example a 4-nitrophenyl ester, or a polyhalophenyl ester, for example a pentachlorophenyl ester (for example by treating with an appropriate hydroxyl compound in the presence of a suitable condensing agent, such as N,N'-dicyclohexylcarbodiimide), and then a reactive derivative of this type can be reacted with an amine and in this way amide compounds of the formula (I) which contain an amidated carboxyl group as a substituent can be obtained. In this case, these can be obtained directly or via intermediate compounds; thus, for example, an activated ester, such as a 4-nitrophenyl ester, of a compound of the formula (I) containing a carboxyl group can first be reacted with a 1-unsubstituted imidazole and the 1-imidazolylcarbonyl compound obtained in this way brought to reaction with an amine. However, other non-activated esters, such as (C_1-C_7)alkyl esters of compounds of the formula (I), which contain, for example, (C_2-C_8)alkoxycarbonyl as a substituent, can also be brought to reaction with amines.

If an aromatic ring contains a hydrogen atom as a substituent, the latter can be replaced by a halogen atom with the aid of a halogenating agent in a customary manner, for example brominated with bromine, hypobromic acid, acyl hypobromites or other organic bromine compounds, for example N-bromosuccinimide, N-bromoacetamide, N-bromophthalimide, pyridinium perbromide, dioxane dibromide, 1,3-dibromo-5,5-dimethylhydantoin or 2,4,4,6-tetrabromo-2,5-cyclohexanedien-1-one, or chlorinated with elemental chlorine, for example in a halogenated hydrocarbon, such as chloroform, and with cooling, for example from down to about -10° to about +100°C.

If an aromatic ring in the compounds according to the invention contains an amino group, this can be diazotized in a customary manner, for example by treating with a nitrite, for example sodium nitrite, in the presence of a suitable protonic acid, for example a mineral acid, the reaction temperature advantageously being kept below about 5°C. The diazonium group present in the salt form and obtainable in this way can be substituted by analogous processes, for example as follows: by the hydroxyl group analogously to the boiling-out of phenol in the presence of water; by an alkoxy group by treating with an appropriate alcohol, energy having to be added; by the fluorine atom analogously to the Schiemann reaction in the thermolysis of corresponding diazonium tetrafluoroborates; by the halogen atoms chlorine, bromine or iodine and also the cyano group analogously to the Sandmeyer reaction in the reaction with corresponding Cu(I) salts, initially with cooling, for example to below about 5°C, and then heating, for example to about 60° to about 150°C.

If the compounds of the formula (I) contain unsaturated radicals, such as (lower) alkenyl or (lower) alkynyl groups, these can be converted into saturated radicals in a manner known per se. Thus, for example, multiple bonds are hydrogenated by catalytic hydrogenation in the presence of hydrogenation catalysts, suitable catalysts for this purpose being, for example, nickel, such as Raney nickel, and noble metals or their derivatives, for example oxides, such as palladium or platinum oxide, which may be applied, if desired, to support materials, for example to carbon or calcium carbonate. The hydrogenation may preferably be carried out at pressures between 1 and about 100 at and at room temperature

between about -80° to about 200°C, in particular between room temperature and about 100°C. The reaction is advantageously carried out in a solvent, such as water, a lower alkanol, for example ethanol, isopropanol or n-butanol, an ether, for example dioxane, or a lower alkanecarboxylic acid, for example acetic acid.

Furthermore, in compounds of the formula (I) in which, for example, one of the aryl radicals contains halogen, such as chlorine, halogen can be replaced by reaction with a substituted or unsubstituted amine, an alcohol or a mercaptan.

The invention relates in particular to the processes described in the examples.

Salts of compounds of the formula (I) can be prepared in a manner known per se. Thus, for example, acid addition salts of compounds of the formula (I) are obtained by treating with an acid or a suitable ion exchange reagent. Salts can be converted into the free compounds in a customary manner, and acid addition salts can be converted, for example, by treating with a suitable basic agent.

Depending on the procedure and reaction conditions, the compounds according to the invention having salt-forming, in particular basic properties, can be obtained in free form or preferably in the form of salts.

In view of the close relationship between the novel compound in the free form and in the form of its salts, in the preceding text and below the free compound or its salts may correspondingly and advantageously also be understood as meaning the corresponding salts or the free compound.

The novel compounds including their salts of salt-forming compounds can also be obtained in the form of their hydrates or can include other solvents used for crystallization.

Depending on the choice of the starting materials and procedures, the novel compounds can be present in the form of one of the possible isomers or as mixtures thereof, for example as pure optical isomers, such as antipodes, or as isomer mixtures, such as racemates, diastereoisomer mixtures or racemate

mixtures, depending on the number of asymmetric carbon atoms. For example, compounds of the formula (I) in which -alk_2-R_2 or -NR_3R_4 have an asymmetric C atom.

Racemates and diastereomer mixtures obtained can be separated into the pure isomers or racemates in a known manner on the basis of the physicochemical differences of the components, for example by fractional crystallization. Racemates obtained may furthermore be resolved into the optical antipodes by known methods, for example by recrystallization from an optically active solvent, chromatography on chiral adsorbents, with the aid of suitable microorganisms, by cleavage with specific immobilized enzymes, via the formation of inclusion compounds, for example using chiral crown ethers, only one enantiomer being complexed, or by conversion into diastereomeric salts, for example by reaction of a basic final substance racemate with an optically active acid, such as a carboxylic acid, for example tartaric or malic acid, or sulfonic acid, for example camphorsulfonic acid, and separation of the diastereomer mixture obtained in this manner, for example on the basis of its differing solubilities, into the diastereomers from which the desired enantiomer can be liberated by the action of suitable agents. The more active enantiomer is advantageously isolated.

The invention also relates to those embodiments of the process, according to which a compound obtainable as an intermediate in any step of the process is used as a starting material and the missing steps are carried out or a starting material in the form of a derivative or salt and/or its racemates or antipodes is used or, in particular, formed under the reaction conditions.

In the process of the present invention, those starting materials are preferably used which lead to the compounds described as particularly useful at the beginning. The invention likewise relates to novel starting materials which have been specifically developed for the preparation of the compounds according to the invention, to their use and to processes for their preparation, the variables alk_1, alk_2, R_1, R_2, R_3, R_4, and X having the meanings indicated for the preferred compound groups of the formula (I) in each case.

The invention likewise relates to pharmaceutical preparations which contain the compounds according to the invention or pharmaceutically acceptable salts thereof as active ingredients, and to processes for their preparation.

The pharmaceutical preparations according to the invention which contain the compound according to the invention or pharmaceutically acceptable salts thereof are those for enteral, such as oral, furthermore rectal, and parenteral administration to (a) warm-blooded animal(s), the pharmacological active ingredient being present on its own or together with a pharmaceutically acceptable carrier. The daily dose of the active ingredient depends on the age and the individual condition and also on the manner of administration.

The novel pharmaceutical preparations contain, for example, from about 10 % to about 80%, preferably from about 20 % to about 60 %, of the active ingredient. Pharmaceutical preparations according to the invention for enteral or parenteral administration are, for example, those in unit dose forms, such as sugar-coated tablets, tablets, capsules or suppositories, and furthermore ampoules. These are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active ingredient with solid carriers, if desired granulating a mixture obtained, and processing the mixture or granules, if desired or necessary, after addition of suitable excipients to give tablets or sugar-coated tablet cores.

Suitable carriers are, in particular, fillers, such as sugars, for example lactose, sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, furthermore binders, such as starch paste, using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, if desired, disintegrants, such as the abovementioned starches, furthermore carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate; auxiliaries are primarily glidants, flow-regulators and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as

magnesium or calcium stearate, and/or polyethylene glycol. Sugar-coated tablet cores are provided with suitable coatings which, if desired, are resistant to gastric juice, using, inter alia, concentrated sugar solutions which, if desired, contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, coating solutions in suitable organic solvents or solvent mixtures or, for the preparation of gastric juice-resistant coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colorants or pigments, for example to identify or to indicate different doses of active ingredient, may be added to the tablets or sugar-coated tablet coatings.

Other orally utilizable pharmaceutical preparations are hard gelatin capsules, and also soft closed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The hard gelatin capsules may contain the active ingredient in the form of granules, for example in a mixture with fillers, such as lactose, binders, such as starches, and/or lubricants, such as talc or magnesium stearate, and, if desired, stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it also being possible to add stabilizers.

Suitable rectally utilizable pharmaceutical preparations are, for example, suppositories, which consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. Furthermore, gelatin rectal capsules which contain a combination of the active ingredient with a base substance may also be used. Suitable base substances are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Suitable preparations for parenteral administration are primarily aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, and furthermore suspensions of the active ingredient, such as appropriate oily injection suspensions, using suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous injection suspensions which contain viscosity-increasing substances, for example sodium

carboxymethylcellulose, sorbitol and/or dextran, and, if necessary, also stabilizers.

The dose of the active ingredient depends on the warm-blooded animal species, the age and the individual condition and on the manner of administration. In the normal case, an approximate daily dose of about 10 mg to about 250 mg is to be estimated in the case of oral administration for a patient weighing approximately 75 kg .

The following examples illustrate the invention described above; however, they are not intended to limit its extent in any manner. Temperatures are indicated in degrees Celsius.

The following examples illustrate the invention.

Abbreviations as used:

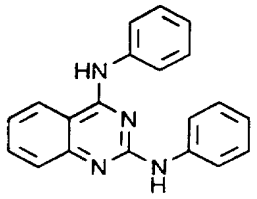
HCl	hydrochloric acid
NaOH	sodium hydroxide
min	minute(s)
h	hour(s)
m.p.	melting point
FAB-MS	Fast Atom Bombardment Mass Spectroscopy
Rf	retention factor on a thin layer chromatography plate

Solvent Systems for Thin-Layer Chromatography:

A1:	dichloromethane / methanol	9:1
A2:	dichloromethane / methanol	19:1
A3:	dichloromethane / methanol / ammonium hydroxide	90:10: 1
B1:	toluene / ethylacetate	1:1
B2:	toluene / ethylacetate	10:1
B3:	toluene / hexanes	1:1
B4:	toluene	
C1:	hexanes / ethylacetate	4:1

C2:	hexanes / ethylacetate	3:1
C3:	hexanes / ethylacetate	2:1
C4:	hexanes / ethylacetate	1:1
D1:	dichloroethane / methanol / water / acetic acid	170:26:3:1
D3:	toluene / ethanol / ammonium hydroxide	90:20: 1
E1:	ethylacetate / ethanol / ammonium hydroxide	6: 3: 1

Example 1: 2,4-Diphenylamino-quinazoline hydrochloride



2-Chloro-4-phenylamino-quinazoline (7.671 g) and aniline (3.627 g) are heated up for 3 min to produce a melt which is dissolved in methanol. The product is obtained as its hydrochloride salt upon addition of a slight excess of 4N HCl in dioxane. Recrystallization from isopropanol yields 2,4-diphenylamino-quinazoline hydrochloride, m.p. 319 - 320°C.

The starting material can be prepared, for example, as follows:

a) 2-Chloro-4-phenylamino-quinazoline

A solution of 2,4-dichloro-quinazoline (15 g), N,N-diisopropyl-ethylamine (24.9 ml) and aniline (7.5 ml) in isopropanol (75 ml) is heated to reflux for 45 min. The cold reaction mixture is filtered and the filtrate is concentrated *in vacuo*. The residue is crystallized from diethylether- toluene (1:1) to give 2-chloro-4-phenylamino-quinazoline, m.p. 194 - 196°C.

b) 2,4-Dichloro-quinazoline

N,N-Dimethylaniline (114.0 g) is added slowly to a solution of 1H,3H-quinazolin-2,4-dione (146.0 g) in phosphorousoxychloride (535.4 ml) while this mixture is heated up to 140°C. After completion of the addition reflux is continued for 20 h . The reaction mixture is filtered and evaporated to give a residue which is added to ice and water. The product is extracted with dichloromethane and crystallized from diethylether and petroleum diethylether to yield 2,4-dichloro-quinazoline, m.p. 115 - 116°C.

Example 2: 2-(4-Methoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.767 g) and 4-methoxy-aniline (0.493 g) is heated up for 3 min to produce a melt which is dissolved in isopropanol (10 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-(4-methoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 296 - 297°C.

Example 3: 2-(4-Fluoro-phenylamino)-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.307 g) and 4-fluoro-aniline (0.144 ml) is heated for 2 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-(4-fluoro-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 322 - 324°C.

Example 4: 2-(4-Phenyl-phenylamino)-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.256 g) and 4-amino-biphenyl (0.211 g) is heated for 2 min to produce a melt which is dissolved in isopropanol (3 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-(4-phenyl-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 306 - 307°C.

Example 5: 2-[4-(N,N-Dimethylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.767 g) and 4-amino-N,N-dimethyl--aniline (0.545 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (10 ml). 4N HCl in dioxane (1 ml) is added. Crystallization yields 2-[4-(N,N-dimethylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, m.p. 281 - 283°C.

Example 6: 2-(3,4-Dimethoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.380 g) and 3,4-dimethoxy-aniline (0.306 g) is heated for 2 min to produce a melt which is dissolved in isopropanol (5 ml). 4N HCl in

dioxane (0.1 ml) is added. Crystallization yields 2-(3,4-dimethoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 250 - 251°C.

Example 7: 2-[4-(N,N-Diethylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.767 g) and 4-amino-N,N-diethyl-aniline (0.657 g) is heated for 2 min to produce a melt which is dissolved in acetonitrile (9 ml) and 4N HCl in dioxane (1 ml). The precipitate is recrystallized from methanol and acetonitrile to yield 2-[4-(N,N-diethylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, m.p. 209 - 211°C.

Example 8: 2-[4-(Benzyloxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.380 g) and 4-benzyloxy-aniline (0.400 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (5 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-[4-(benzyloxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride, m.p. 225 - 227°C.

Example 9: 2-(4-Amino-phenylamino)-4-phenylamino-quinazoline dihydrochloride

A solution of 2-(4-nitro-phenylamino)-4-phenylamino-quinazoline (0.536 g) in N,N-dimethylformamide (15 ml) is hydrogenated in the presence of Raney nickel (3 times 0.2 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The obtained residue is dissolved in isopropanol - methanol (1:1) (10 ml) and treated with 4N HCl in dioxane (1 ml). Crystallization yields 2-(4-amino-phenylamino)-4-phenylamino-quinazoline dihydrochloride, m.p. 311 - 312°C.

The starting material can be prepared, for example, as follows:

2-(4-Nitro-phenylamino)-4-phenylamino-quinazoline

A mixture of 2-chloro-4-phenylamino-quinazoline (0.511 g) and 4-nitro-aniline (0.332 g) is heated for 2 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in

dioxane (0.1 ml) is added. Crystallization yields 2-(4-nitro-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 348-350°C.

Example 10: 2-[3-(N,N-Dimethylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.384 g) and 3-amino-N,N-dimethyl-aniline (0.272 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in dioxane (1 ml) is added. Crystallization yields 2-[3-(N,N-dimethylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, m.p. 280 - 283°C.

Example 11: 2-[4-(N,N-Dipropylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (1.40 g) and 4-amino-N,N-dipropyl-aniline (1.37 g) is heated for 5 min to produce a melt which is dissolved in isopropanol (16 ml). 4N HCl in dioxane (1.5 ml) is added. Crystallization yields 2-[4-(N,N-dipropylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, m.p. 270 - 272°C.

The starting material can be prepared, for example, as follows:

a) 4-Nitro-N,N-dipropyl-aniline
A mixture of 4-fluoro-1-nitro-benzene (1.41 g) and dipropylamine (6.86 ml) is heated in an autoclave for 8 h to 160°C. The product is added to 2N aqueous NaOH and extracted with ethylacetate to yield 4-nitro-N,N-dipropyl-aniline as a yellowish oil, Rf (C3) 0.59.

b) 4-Amino-N,N-dipropyl-aniline
A solution of 4-nitro-N,N-dipropyl-aniline (2.2 g) in ethanol (50 ml) is hydrogenated in the presence of Raney nickel (3 times 0.5 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo* to yield of 4-amino-N,N-dipropyl-aniline as an oil, Rf (C3) 0.09.

Example 12: 2-(4-Cyano-phenylamino)-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.511 g) and 4-amino-benzonitrile (0.315 g) is heated for 2 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-(4-cyano-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 340 - 342°C.

Example 13: 2-[4-(2-Pyridylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.384 g) and 4-(2-pyridylamino)-aniline (0.334 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in dioxane (1 ml) is added. Crystallization yields 2-[4-(2-pyridylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, m.p. 225 - 226°C.

The starting material can be prepared, for example, as follows:

4-(2-Pyridylamino)-aniline

A solution of N-(4-nitrophenyl)-2-pyridinamine (*Annali di Chimia* **1956**, *46*, 406) (5.38 g) in ethanol (100 ml) is hydrogenated in the presence of palladium on charcoal 5% (0.5 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo* to yield 4-(2-pyridylamino)-aniline, m.p. 120 - 122°C.

Example 14: 2-[4-(Aminomethyl)-phenylamino]-4-phenylamino-quinazoline dihydrochloride

A solution of 2-(4-cyano-phenylamino)-4-phenylamino-quinazoline hydrochloride (5.42 g) in ethanol (20 ml) is hydrogenated in the presence of Raney nickel (0.3 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The residue is treated with 4N HCl in dioxane (2 ml) and crystallized from isopropanol and methanol to yield of 2-[4-(aminomethyl)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, m.p. 320 - 322°C.

Example 15: 2-[3-(Aminomethyl)-phenylamino]-4-phenylamino-quinazoline dihydrochloride

A solution of 2-(3-cyano-phenylamino)-4-phenylamino-quinazoline hydrochloride (0.939 g) in ethanol (40 ml) is hydrogenated in the presence of Raney nickel (0.5 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The residue is treated with 4N HCl in dioxane (3 ml) and crystallized from isopropanol and methanol to yield of 2-[3-(aminomethyl)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, m.p. 280 - 282°C.

The starting material can be prepared, for example, as follows:

2-(3-Cyano-phenylamino)-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.770 g) and 3-amino-benzonitrile (0.460 g) is heated for 5 min to produce a melt which is dissolved in isopropanol (10 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-(3-cyano-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 326 - 328°C.

Example 16: 2-(4-Hydroxy-phenylamino)-4-phenylamino-quinazoline hydrochloride

A solution of 2-[4-(phenylmethyloxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride (2.15 g) in ethanol (50 ml) is hydrogenated in the presence of palladium on charcoal 5% (0.6 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The residue is crystallized from isopropanol and methanol to yield 2-(4-hydroxy-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 309 - 310°C.

The starting material can be prepared, for example, as follows:

2-[4-(Phenylmethyloxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (1.28 g) and 4-benzyloxy-aniline (1.33 g) is heated for 5 min to produce a melt which is dissolved in isopropanol (15 ml). 4N HCl in dioxane (0.2 ml) is added. Crystallization yields 2-[4-(phenylmethyloxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride, m.p. 225 - 226°C.

Example 17: 2-[4-(3-Cyclohexyl-propyloxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride

A suspension of 2-(4-hydroxy-phenylamino)-4-phenylamino-quinazoline hydrochloride (292 g), 3-iodopropyl-cyclohexane (EP 518,426) (0.212 g), and potassium carbonate (0.221 g) in acetonitrile (20 ml) is heated to reflux for 5 h. The raction mixture is filtered and the filtrate concentrated *in vacuo*. The residue is added to 2N NaOH and extracted with ethylacetate. The crude product is treated with 4N HCl in dioxane and crystallized from isopropanol and acetonitrile to yield
2-[4-(3-cyclohexyl-propyloxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride, m.p. 223 - 224°C.

Example 18: 2,4-Di-(4-methoxy-phenylamino)-quinazoline hydrochloride

A mixture of 2-chloro-4-(4-methoxy-phenylamino)-quinazoline (0.50 g) and 4-methoxy--aniline (0.28 g) is heated for 4 min to produce a melt which is dissolved in isopropanol (5 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2,4-di-(4-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 282 - 284°C.

The starting material can be prepared, for example, as follows:

2-Chloro-4-(4-methoxy-phenylamino)-quinazoline
A solution of 2,4-dichloro-quinazoline (4.0 g), N,N-diisopropyl-ethylamine (6.6 ml) and 4-methoxy-aniline (2.5 g) in isopropanol (20 ml) is heated to reflux for 20 min. The reaction mixture is concentrated *in vacuo* and the residue is added to 2N sodium bicarbonate and extracted with ethylacetate. Crystallization from toluene gives 2-chloro-4-(4-methoxy-phenylamino)-quinazoline, m.p. 150 - 152°C.

Example 19: 2-(4-Cyano-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride

A mixture of 2-chloro-4-(3-methoxy-phenylamino)-quinazoline (0.429 g) and 4-amino-benzonitrile (0.236 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-(4-cyano-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 274 - 276°C.

The starting material can be prepared, for example, as follows:

2-Chloro-4-(3-methoxy-phenylamino)-quinazoline

A solution of 2,4-dichloro-quinazoline (6.0 g), N,N-diisopropyl-ethylamine (9.95 ml),and 3-methoxy-aniline (3.68 ml) in isopropanol (30 ml) is heated to reflux for 30 min. The reaction mixture is concentrated *in vacuo* and the residue is added to 2N NaOH and extracted with ethylacetate. Crystallization from toluene gives 2-chloro-4-(3-methoxy-phenylamino)-quinazoline, m.p. 176 - 178°C.

Example 20: 2-[4-(N,N-Diethylamino)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline dihydrochloride

A mixture of 2-chloro-4-(3-methoxy-phenylamino)-quinazoline (0.286 g) and 4-amino-N,N-diethyl-aniline (0.214 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (3 ml) and 4N HCl in dioxane (1 ml). The precipitate is recrystallized from isopropanol and diethylether to yield 2-[4-(N,N-diethylamino)-phenylamino]-4-(3-methoxy--phenylamino)-quinazoline dihydrochloride, m.p. 239 - 241°C.

Example 21: 2-(4-Cyclohexyl-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride

A mixture of 2-chloro-4-(3-methoxy-phenylamino)-quinazoline (0.286 g) and 4-cyclohexyl-aniline (0.228 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (3 ml) and 4N HCl in dioxane (0.1 ml). Recrystallisation from isopropanol and diethylether yields 2-(4-cyclohexyl-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 240 - 242°C.

Example 22: 2-(4-Methoxy-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride

A mixture of 2-chloro-4-(3-methoxy-phenylamino)-quinazoline (0.286 g) and 4-methoxy-aniline (0.160 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (3 ml) and 4N HCl in dioxane (0.1 ml). Crystallization from isopropanol and diethylether yields

2-(4-methoxy-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 271 - 272°C.

Example 23: 2-[4-(Aminomethyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline dihydrochloride

A solution of 2-(4-cyano-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride (0.38 g) in ethanol (20 ml) is hydrogenated in the presence of Raney nickel (0.2 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The residue is dissolved in methanol and treated with 4N HCl in dioxane (1 ml) and crystallized from isopropanol and methanol to yield 2-[4-(aminomethyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline dihydrochloride, m.p. 215 - 217°C.

Example 24: 2-(4-N,N-Diethylamino-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride

A mixture of 2-chloro-4-(4-methoxy-phenylamino)-quinazoline (0.429 g) and 4-amino-N,N-diethyl-aniline (0.320 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (5 ml) and 4N HCl in dioxane (1 ml). Crystallization from isopropanol and acetonitrile yields 2-(4-N,N-diethylamino-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride, m.p. 238 - 240°C.

Example 25: 2-[4-(N,N-Dipropylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride

A mixture of 2-chloro-4-(4-methoxy-phenylamino)-quinazoline (0.57 g) and 4-amino-N,N-dipropyl-aniline (0.50 g) is heated for 4 min to produce a melt which is dissolved in isopropanol (6 ml). 4N HCl in dioxane (1 ml) is added. Crystallization from isopropanol and acetonitrile yields 2-[4-(N,N-dipropylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride, m.p. 246 - 248°C.

Example 26: 2-(4-Cyclohexyl-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline hydrochloride

A mixture of 2-chloro-4-(4-methoxy-phenylamino)-quinazoline (0.343 g) and 4-cyclohexyl-aniline (0.274 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (4 ml) and 4N HCl in dioxane (0.1 ml). Recrystallisation from isopropanol and diethylether yields 2-(4-cyclohexyl-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 301 - 302°C.

Example 27: 2-(4-Hydroxy-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline hydrochloride

A solution of 2-[4-(phenylmethyloxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride (0.582 g) in methanol (20 ml) is hydrogenated in the presence of palladium on charcoal 5% (0.12 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The residue is crystallized from isopropanol and methanol to yield 2-(4-hydroxy-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 256 - 258°C.

The starting material can be prepared, for example, as follows:

2-[4-(Phenylmethyloxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride
A mixture of 2-chloro-4-(4-methoxy-phenylamino)-quinazoline (0.571 g) and 4-benzyloxy-aniline (0.517 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (6 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-[4-(phenylmethyloxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 272 - 273°C.

Example 28: 2-[4-(2-Pyridylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride

A mixture of 2-chloro-4-(4-methoxy-phenylamino)-quinazoline (0.256 g) and 4-(2-pyridylamino)-aniline (0.280 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in dioxane (1 ml) is added. Crystallization from methanol and isopropanol yields 2-[4-(2-pyridylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride, m.p. 240 - 242°C.

Example 29: 2-[4-(N,N-Dimethylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride

A mixture of 2-chloro-4-(4-methoxy-phenylamino)-quinazoline (0.429 g) and 4-amino-N,N-dimethyl-aniline (0.273 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (5 ml). 4N HCl in dioxane (1 ml) is added. Crystallization yields 2-[4-(N,N-dimethylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride, m.p. 228 - 230°C.

Example 30: 2-[4-(Piperidin-1-yl)-phenylamino]-4-phenylamino-quinazoline dihydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.18 g) and N-(4-aminophenyl)-piperidine (0.164 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in dioxane (1 ml) is added. Recrystallization from ethanol and diethylether yields 2-[4-(piperidin-1-yl)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, Rf (A1) 0.64.

Example 31: 2-[4-(Benzyloxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride

A mixture of 2-chloro-4-(3-methoxy-phenylamino)-quinazoline (1.99 g) and 4-benzyloxy-aniline (1.80 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (6 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization from isopropanol and diethylether yields 2-[4-(benzyloxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 206 - 207°C.

Example 32: 2-(4-Hydroxy-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride

A solution of 2-[4-(benzyloxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride (1.80 g) in methanol (50 ml) is hydrogenated in the presence of palladium on charcoal 5% (0.36 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated in vacuo. The residue is crystallized from methanol

and acetonitrile to yield 2-(4-hydroxy-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 281 - 283°C.

Example 33: 2-[3-(N,N-Dimethylamino)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline dihydrochloride

A mixture of 2-chloro-4-(3-methoxy-phenylamino)-quinazoline (0.57 g) and 3-amino-N,N-dimethyl-aniline (0.35 g) is heated for 4 min to produce a melt which is dissolved in isopropanol (6 ml). 4N HCl in dioxane (1 ml) is added. Crystallization yields 2-[3-(N,N-dimethylamino)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline dihydrochloride, m.p. 197 - 199°C.

The following compounds are prepared, for example, in an analogous manner:

Example 34: 2-(4-Chloro-phenylamino)-4-phenylamino-quinazoline hydrochloride
M.p. 325 - 326°C.

Example 35: 2-(4-Methyl-phenylamino)-4-phenylamino-quinazoline hydrochloride
M.p. 294 - 296°C.

Example 36: 2-(3-Methoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride
M.p. 298 - 299°C.

Example 37: 2-(2-Methoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride
M.p. 256 - 258°C.

Example 38: 2-(4-Nitro-phenylamino)-4-phenylamino-quinazoline hydrochloride
M.p. 348 - 350°C.

Example 39: 2,4-Di-(3-methoxy-phenylamino)-quinazoline hydrochloride
M.p. 232 - 233°C.

Example 40: 2-[4-(Benzyloxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride

M.p. 272 - 273°C.

Example 41: 2-[4-(Aminomethyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride

M.p. 308 - 311°C.

Example 42: 2-[4-(Piperidin-1-yl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride

M.p. 230 - 233°C.

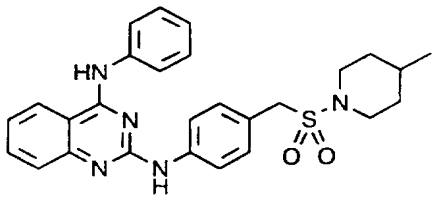
Example 43: 2-[4-(Piperidin-1-yl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride

M.p. 282 - 285°C.

Example 44: N-Methyl-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methane sulfonamide hydrochloride

A solution of 2-chloro-4-phenylamino-quinazoline (0.92 g) (prepared as described in Example 1a and N-methyl-(4-aminophenyl)-methanesulfonamide (0.80 g) (prepared as described in *Tetrahedron Letters* **1992,** *33*, 8011) in 10 ml of isopentylalcohol is stirred under nitrogen at 170 °C for 15 min in a sealed vessel. The warm reaction mixture is diluted with 10 ml ethanol and the hydrochloride salt, which is crystallizing on cooling, is filtered off to yield N-methyl-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as light yellow crystals melting at 259 - 263°C; Rf (A2) 0.11.

Example 45: N-2-[4-(4-Methyl-piperidine-1-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine hydrochloride



In a procedure analogous to that of Example 44 2-chloro-4-phenylamino-quinazoline (0.312 g) and N-(4-methyl-piperidine-1-sulfonylmethyl)-phenylamine (0.36 g) are reacted together to give after recrystallisation from dimethylformamide and diethylether N-2-[4-(4-methyl-piperidine-1-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine hydrochloride as yellow crystals melting at 234 - 238°C; Rf (A2) 0.14; FAB-MS: $(M+H)^+ = 488$.

The starting material can be prepared, for example, as follows:

a) 4-Methyl-1-(4-nitro-benzylsulfonyl)-piperidine

A solution of (4-nitrophenyl)-methanesulfonylchloride (3.54 g) (prepared as described in *J. Am. Chem. Soc.* **1937**,*59*,1837) in dichloromethane (50 ml) is added to a solution of 4-methyl-piperidine (3.8 ml) in 25 ml of dichloromethane at 0 - 5°C and the reaction mixture is stirred for 20 h at room temperature. The solvent is evaporated and the residue is dissolved in ethylacetate (100 ml) and washed with water. The organic layer is dried, concentrated and the crude product is recrystallised from ethylacetate and diethylether to yield 4-methyl-1-(4-nitro-benzylsulfonyl)-piperidine as white crystals melting at 136 - 138°C; Rf (B1) 0.54.

b) 4-(4-methyl-piperidine-1-sulfonylmethyl)-phenylamine

A solution of 4-methyl-1-(4-nitro-phenylmethanesulfonyl)-piperidine (3.8 g) in methanol (300 ml) is hydrogenated over 5% palladium on carbon (0.75 g) at 3 atm. and 25°C for 2 h. The reaction mixture is filtered, partly concentrated and crystallized by the addition of diethylether to yield 4-(4-methyl-piperidine-1-sulfonylmethyl)-phenylamine, melting at 138 - 139°C; Rf (B1) 0.39.

Example 46: N-2-[4-(N-Methyl-piperazine-1-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine dihydrochloride

In a procedure analogous to that of Example 44 2-chloro-4-phenylamino-quinazoline (0.228 g) and N-[N-methyl-piperazinyl-(4-aminophenyl)]-methanesulfonamide monohydrochloride (0.3 g) are reacted together to give N-2-[4-(N-methyl-piperazine-1-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine dihydrochloride as yellow crystals melting at 206 - 209°C; Rf (A2) 0.05.

The starting material can be prepared, for example, as follows:

a) 1-Methyl-4-(4-nitro-phenylmethanesulfonyl)-piperazine
In a procedure analogous to that of Example 45a (4-nitrophenyl)-methanesulfonylchloride (3.54 g) and 4-methyl-piperazine (3.6 ml) are reacted together to give 1-Methyl-4-(4-nitro-phenyl-methanesulfonyl)-piperazine melting at 189 - 192°C; Rf (D3) 0.39.

b) 4-(4-methyl-piperazine-1-sulfonylmethyl)-phenylamine
In a procedure analogous to that of Example 45b 1-Methyl-4-(4-nitro-phenylmethane-sulfonyl)-piperazine (4.35 g) is hydrogenated over 5% palladium on carbon (0.8 g) to yield 4-(4-methyl-piperazine-1-sulfonylmethyl)-phenylamine , melting at 136 - 137°C. After addition of 1 equivalent of HCl to a methanolic solution of the free base 4-(4-methyl-piperazine-1-sulfonylmethyl)-phenylamine monohydrohloride is crystallized, melting at 167 - 169°C; Rf (D3) 0.30.

Example 47: N-2-[4-(Morpholine-4-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine hydrochloride

In a procedure analogous to that of Example 44 2-chloro-4-phenylamino-quinazoline (0.18 g) and 4-(morpholine-4-sulfonylmethyl)-phenylamine (0.19 g) are reacted together to give N-2-[4-(morpholine-4-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine hydrochloride as yellow crystals melting at 268 - 272°C; Rf (A2) 0.22.

The starting material can be prepared, for example, as follows:

a) 4-(4-Nitro-phenylmethanesulfonyl)-morpholine
In a procedure analogous to that of Example 45a (4-nitrophenyl)-methanesulfonylchloride (5.0 g) and morpholine (4.06 g) are reacted together to give 4-(4-nitrophenyl-methanesulfonyl)-morpholine melting at 171 - 172°C; Rf (A2) 0.65.

b) 4-(Morpholine-4-sulfonylmethyl)-phenylamine

In a procedure analogous to that of Example 45b 4-(4-nitro-phenylmethanesulfonyl)--morpholine (5.32 g) is hydrogenated over 5% palladium on carbon (0.5 g) to yield 4-(morpholine-4-sulfonylmethyl)-phenylamine, melting at 166 - 167°C; Rf (A2) 0.47.

Example 48: N,N-Dimethyl-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride

A solution of 2-chloro-4-phenylamino-quinazoline (0.32 g) (prepared as described in Example 1a and N,N-dimethyl-[4-amino-phenyl]-methanesulfonamide (0.29 g) (prepared as described in the GB 82-16526) in 5 ml of isopentylalcohol is stirred under nitrogen at 155°C for 10 min in a sealed vessel. The crude product, which is crystallizing on cooling, is filtered off, redissolved in ethylacetate and aqueous sodium carbonate solution and extracted with ethylacetate. The organic extracts are dried and concentrated and the solid residue is titurated with diethylether to give 0.3 g of N,N-dimethyl-[4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide as light yellow crystals melting at 247 - 249°C; Rf (A2) 0.24. Recrystallisation from methanolic HCl and diethylether yields N,N-dimethyl-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as light yellow crystals melting at 257 - 260°C.

Example 49: N-(2-Methoxy-ethyl)-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride

In a procedure analogous to that of Example 44 2-chloro-4-phenylamino-quinazoline (0.18 g) and N-(2-methoxy-ethyl)-(4-amino-phenyl)-methanesulfonamide (0.184 g) are reacted together to give N-(2-methoxy-ethyl)-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride of as colorless crystals melting at 266 - 270°C; Rf (A2) 0.18.

The starting material can be prepared, for example, as follows:

a) N-(2-Methoxy-ethyl)-(4-nitro-phenyl)-methanesulfonamide
In a procedure analogous to that of Example 45a (4-nitro-phenyl)-methanesulfonylchloride (5 g) and 2-methoxy-ethylamine (3.5 g) are reacted together to give N-(2-methoxy-ethyl)-(4-nitro-phenyl)-methanesulfonamide melting at 91 - 92°C; Rf (A2) 0.49.

b) N-(2-Methoxy-ethyl)-(4-amino-phenyl)-methanesulfonamide

In a procedure analogous to that of Example 45b N-(2-methoxy-ethyl)-(4-nitro-phenyl)]-methanesulfonamide (5 g) is hydrogenated over 5% palladium on carbon to yield N-(2-methoxy-ethyl)-(4-amino-phenyl)-methanesulfonamide melting at 78 - 80°C; Rf (A2) 0.23.

Example 50: 2-[4-(Ethanesulfonylmethyl)-phenylamino]-4-phenylamino-quinazoline hydrochloride

In a procedure analogous to that of Example 44 2-chloro-4-phenylamino-quinazoline (0.563 g) and 4-ethanesulfonylmethyl-phenylamine (prepared as described in *I. G. Farbenind.* **1934**, 623883) (0.368 g) are reacted together to give 2-[4-(ethanesulfonylmethyl)-phenylamino]-4-phenylamino-quinazoline hydrochloride of as colorless crystals melting at 260°C with decompostion; Rf (A2) 0.18, FAB-MS:$(M+H)^+$ 419.

Example 51: N-{4-[4-(4-Methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl}-methanesulfonamide hydrochloride

A suspension of 2-[4-(aminomethyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline (Example 23) (0.41 g) and methanesulfonyl chloride (0.095 ml) in dichloromethane -dioxane (1:1) (10 ml) is stirred at ambient temperature for 16 h. The precipitate is collected by filtration and treated with 4N HCl in dioxane (1 ml) to give N-{4-[4-(4-methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl}-methanesulfonamide hydrochloride, m.p. 275 - 277°C.

The starting material can be prepared, for example, as follows:

a) 2-[4-(Aminomethyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride

A solution of 2-(4-cyano-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline hydrochloride (1.00 g) in ethanol (50 ml) is hydrogenated in the presence of Raney nickel (0.5 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The residue is dissolved in methanol and treated with 4N HCl in dioxane (2 ml) and crystallized from isopropanol and diethylether to yield 2-[4-

(aminomethyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride, m.p. 308 - 311°C.

b) 2-(4-Cyano-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline hydrochloride
A mixture of 2-chloro-4-(4-methoxy-phenylamino)-quinazoline (1.143 g) and 4-amino-benzonitrile (0.614 g) is heated for 4 min to produce a melt which is dissolved in isopropanol (15 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-(4-cyano-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 340 - 342°C.

Example 52: N-{4-[4-(3-Methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl}-methanesulfonamide hydrochloride

A suspension of 2-[4-(aminomethyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline (Example 23) (0.371 g) and methane-sulfonyl chloride (0.086 ml) in dichloromethane (10 ml) and dioxane (5 ml) is stirred at ambient temperature for 16 h. The precipitate is collected by filtration and is suspended in 2N NaOH. The base is extracted with ethylacetate and treated with 4N HCl in dioxane (1 ml) to give N-{4-[4-(3-methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl}-methanesulfonamide hydrochloride, m.p. 220 - 222°C.

In analogous manner can be prepared:

Example 53: N-[4-(4-Phenylamino-quinazolin-2-ylamino)-benzyl]-methanesulfonamide hydrochloride

M.p. 179 - 181°C.

Example 54: 2-(4-Cyclohexyl-phenylamino)-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.38 g) and 4-cyclohexyl-aniline (0.35 g) is heated for 3 min to produce a melt which is dissolved in ethanol (5 ml) and 4 N HCl in dioxane (0.1 ml). Crystallisation from ethanol and diethylether yields 2-(4-cyclohexyl-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 291 - 293°C.

Example 55: 6-Bromo-2,4-di-(3-methoxy-phenylamino)-quinazoline hydrochloride

In a procedure analogous to that of Example 44 6-bromo-2-chloro-4-(3-methoxy-phenylamino)-quinazoline (prepared as described in *Khim.-Farm. Zh.* **1987**, *21*, 802) (0.278 g) and 3-methoxy-aniline (0.25 ml) are reacted together to give 6-bromo-2,4-di-(3-methoxy-phenylamino)-quinazoline hydrochloride as orange crystals melting at 220 - 228°C; Rf (B1) 0.61.

Example 56: 2-(3-Methoxy-phenylamino)-6-nitro-4-phenylamino-quinazoline hydrochloride)

In a procedure analogous to that of Example 44 2-chloro-6-nitro-4-phenylamino-quinazoline (0.527 g) and 3-methoxy-aniline (0.215 ml) are reacted together to give 2-(3-methoxy-phenylamino)-6-nitro-4-phenylamino-quinazoline hydrochloride as brown-orange crystals melting at 247 - 252°C; Rf (A2) 0.55.

The starting material can be prepared, for example, as follows:

2-Chloro-6-nitro-4-phenylamino-quinazoline

In a procedure analogous to that of Example 1a 2,4-dichloro-6-nitro-quinazoline (2.0 g) (prepared as described in JP 78-79950), aniline (0.91 g) (0.184 g) and N,N-diisopropyl-ethylamine (2.1 g) are reacted together to give 2-chloro-6-nitro-4-phenylamino-quinazoline as light yellow crystals melting at 246 - 248°C; Rf (A2) 0.65.

Example 57: 6-Amino-2-(3-methoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride

In a procedure analogous to that of Example 9 2-(3-methoxy-phenylamino)-6-nitro-4-phenylamino-quinazoline hydrochloride (Example 61) (0.435 g) is hydrogenated in the presence of Raney nickel (0.1 g) at ambient temperature and pressure to give 6-amino-2-(3-methoxy-phenylamino)-4-phenylamino-quinazoline dihydrochloride as light-yellow crystals melting at 269 - 273°C; Rf (A1) 0.18.

Example 58: 2,4-Diphenylamino-6-phenyl-quinazoline

A solution of 2,4-dichloro-6-phenyl-quinazoline (0.78 g) and aniline (0.54 ml) in 5 ml of ethanol is stirred under nitrogen at 60°C for 1 h. The crude product, which is crystallizing on cooling, is filtered off, redissolved in ethylacetate and aqueous 1 N NaOH solution and extracted with ethylacetate. The organic extracts are dried, evaporated and the oily residue is chromatographed on silica gel (elution with dichloromethane). Crystallization from methanol yields 2,4-diphenylamino-6-phenyl-quinazoline as colorless crystals melting at 145 - 147°C; Rf (A2) 0.59.

The starting material can be prepared, for example, as follows:

a) 4-Amino-biphenyl-3-carboxylic acid

To a suspension of 2-amino-5-bromo-benzoic acid (10.0 g) in toluene (150 ml) and water (20 ml) is added under an argon atmosphere cesium carbonate (22.0 g), phenylboronic acid (8.2 g) and tetrakis-(triphenylphosphine)-palladium (1.2 g) and the reaction mixture is stirred at reflux temperature for 24 h. The organic layer is separated and washed with 0.1 N aqueous NaOH and water and then decolorized with charcoal and filtered. The colorless filtrate is acidified with aqueous HCl and the precipitate is collected, washed with water and dried to yield 4-amino-biphenyl-3-carboxylic acid as a tan powder melting at 207 - 210°C; Rf (A1) 0.45.

b) 6-Phenyl-quinazolin-2,4-dione

To a suspension of 4-amino-biphenyl-3-carboxylic acid (6.7 g) in dioxane (50 ml), water (30 ml), and acetic acid (3.6 ml) is added a solution of potassium cyanate (6.1 g) in water (20 ml) at 15 - 20°C and the reaction mixture is stirred for 2 h at 25°C. After addition of solid NaOH (7.54 g) the suspensionn is heated at reflux for 3 h. The reaction mixture is cooled to 0°C, diluted with ice-water (200 ml) and acidified with 2 N HCl. The colorless precipitate is filtered off, washed with ice-water and dried to give 6-phenyl-quinazolin-2,4-dione as a white powder melting at > 300°C; Rf (A1) 0.41.

c) 2,4-Dichloro-6-phenyl-quinazoline

To a suspension of 6-phenyl-quinazolin-2,4-dione (4.5 g) and N,N-dimethylaniline (4.1 ml) in toluene (100 ml) is added slowly phosphorousoxychloride (8.7 ml) and the reaction mixture is heated at reflux for 16 h. The reaction mixture is poured into ice-water, diluted with ethylacetate (200 ml) and the product is extracted with ethylacetate. The organic

extracts are washed with water and 5% aqueous sodium bicarbonate solution, dried and evaporated. The residue is crystallized from diethylether to yield 2,4-dichloro-4-phenyl-quinazoline, m.p. 142 - 144°C; Rf (B2) 0.59.

Example 59: N,N-Dimethyl-[4-(6-phenyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride

In a procedure analogous to that of Example 44 2-chloro-6-phenyl-4-phenylamino-quinazoline (0.177 g) and N,N-dimethyl-(4-aminophenyl)-methanesulfonamide (0.125 g) are reacted together to give N,N-dimethyl-[4-(6-phenyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as yellow crystals melting at 258 - 263°C; Rf (A2) 0.40.

Example 60: N,N-Dimethyl-[4-(5-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride

A solution of 2-chloro-5-methoxy-4-phenylamino-quinazoline (0.17 g) and N,N-dimethyl-(4-aminophenyl)-methanesulfonamide (0.14 g) in 3 ml of isopentylalcohol is stirred under nitrogen at 160°C for 5 min in a sealed vessel. The warm reaction mixture is diluted with 10 ml ethanol and the hydrochloride salt, which is crystallizing on cooling, is filtered off to yield N,N-dimethyl-[4-(5-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methane-sulfonamide hydrochloride as light yellow crystals melting at 233 - 236°C; Rf (A2) 0.21.

The starting material can be prepared, for example, as follows:

2-Chloro-5-methoxy-4-phenylamino-quinazoline

To a suspension of 2,4-dichloro-5-methoxy-quinazoline (1 g) (prepared as described in *J. Chem. Soc.* **1948**, 1759), N,N-diisopropyl-ethylamine (5.0 ml) and isopropanol (10 ml) is added aniline (0.48 g) and the reaction mixture is heated at 70°C for 0.5 h. The product which is crystallizing on cooling, is filtered off and recrystallized from ethanol to yield 2-chloro-5-methoxy-4-phenylamino-quinazoline as light yellow crystals melting at 191 - 192°C; Rf (B2) 0.12.

Example 61: N-Methyl-[4-(6-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride

A solution of 2-chloro-6-methoxy-4-phenylamino-quinazoline (1.15 g) and N-methyl-(4-aminophenyl)-methanesulfonamide (0.89 g) in 5 ml of isopentylalcohol is stirred under nitrogen at 180°C for 20 min in a sealed vessel. The warm reaction mixture is diluted with methanol and the hydrochloride salt, which is crystallizing on cooling, is filtered off. The crude product is redissolved in ethylacetate and aqueous sodium carbonate solution and extracted with ethylacetate. The organic extracts are dried and evaporated and the solid residue is titurated with diethylether to give N-methyl-[4-(6-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide as light yellow crystals melting at 212 - 215°C; (Rf (A2) 0.16. Recrystallisation from methanolic hydrogen chloride and diethylether yields N-methyl-[4-(6-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methane-sulfonamide hydrochloride as light yellow crystals melting at 264 - 268°C; Rf (A2) 0.16.

The starting material can be prepared, for example, as follows:

2-Chloro-6-methoxy-4-phenylamino-quinazoline

In a procedure analogous to that of Example 60 2,4-dichloro-6-methoxy-quinazoline (1.53 g) (prepared as described in *J. Chem. Soc.* **1948**, 1759), aniline (0.8 g) (0.184 g) and N,N-diisopropyl-ethylamine (1.72 g) are reacted together to give 2-chloro-6-methoxy-4-phenylamino-quinazoline as light yellow crystals melting at 177 - 179°C; Rf (A2) 0.59.

Example 62: 6-Methoxy-2-(4-methoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride

In a procedure analogous to that of Example 61 2-chloro-6-methoxy-4-phenylamino-quinazoline (0.221 g) and 4-methoxy-aniline (0.114 g) are reacted together to give 6-methoxy-2-(4-methoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride as light yellow crystals melting at 239 - 242°C; Rf (A2) 0.23.

Example 63: 2-(4-Hydroxy-phenylamino)-6-methoxy-4-phenylamino-quinazoline hydrochloride

In a procedure analogous to that of Example 61 2-chloro-6-methoxy-4-phenylamino-quinazoline (0.141 g) and 4-amino-phenol (0.064 g) are reacted together to give 2-(4-hydroxy-phenylamino)-6-methoxy-4-phenylamino-quinazoline hydrochloride as yellow crystals melting at 304 - 308°C; Rf (A2) 0.05.

Example 64: 2-(4-Benzyloxy-phenylamino)-6-methoxy-4-phenylamino-quinazoline hydrochloride

In a procedure analogous to that of Example 61 2-chloro-6-methoxy-4-phenylamino-quinazoline (0.162 g) and 4-benzyloxyaniline (0.135 g) are reacted together to give 2-(4-benzyloxy-phenylamino)-6-methoxy-4-phenylamino-quinazoline hydrochloride as brown crystals melting at 269 - 274°C; Rf (A2) 0.22.

Example 65: N-Methyl-[4-(7-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride

A solution of 2-chloro-7-methoxy-4-phenylamino-quinazoline (0.105 g) (prepared as described in *J. Chem. Soc.* **1948**, 1759) and N-methyl-[4-amino-phenyl]-methane-sulfonamide (0.082 g) in 2 ml of isopentylalcohol is stirred under nitrogen at 170°C for 5 min in a sealed vessel. The warm reaction mixture is diluted with 5 ml ethanol and the hydrochloride salt, which is crystallizing on cooling, is filtered off, to yield N-methyl-[4-(7-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as colorless crystals melting at 273 - 277°C; Rf (A2) 0.11.

Example 66: N-Methyl-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride

A mixture of 2-chloro-8-methoxy-4-phenylamino-quinazoline (0.598 g) and N-methyl-(4-aminophenyl)-methanesulfonamide (prepared as described in Tetrahedron Letters **1992,** *33*, 8011) (0.540 g) is heated for 2 min to produce a melt which is dissolved in isopropanol (5 ml). Crystallization from isopropanol and diethylether yields N-methyl-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride, m.p. 289 - 290°C.

The starting material can be prepared, for example, as follows:

2-Chloro-8-methoxy-4-phenylamino-quinazoline

A solution of 2,4-dichloro-8-methoxy-quinazoline (prepared as described in *J. Chem. Soc.* **1948**, 1759) (0.6 g), N,N-diisopropyl-ethylamine (0.87 ml), and aniline (0.26 ml) in isopropanol (10 ml) is heated to reflux for 45 min. The cold reaction mixture is filtered and residue is crystallized from dichloromethane and hexanes to give 2-chloro-8-methoxy-4-phenylamino-quinazoline, m.p. 245 - 246°C.

The following compounds are prepared in an analogous manner:

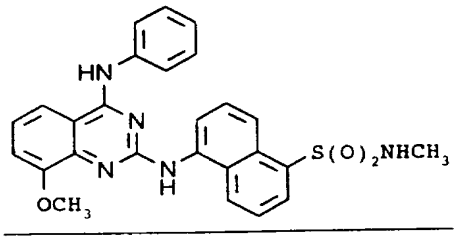
Example 67: N-[4-(8-Methoxy-4-phenylamino-quinazolin-2-ylamino)-benzyl]-methanesulfonamide hydrochloride

Rf(A1) 0.45.

Example 68: N-{4-[8-Methoxy-4-(3-methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl}-methanesulfonamide hydrochloride

Rf(A1) 0.52.

Example 69: 5-[8-Methoxy-4-phenylamino-quinazolin-2-ylamino)-naphthalene-1-sulfonic acid methylamide hydrochloride



A mixture of 2-chloro-8-methoxy-4-phenylamino-quinazoline (0.427 g) and 5-amino-naphthalene-1-sulfonic acid methylamide (0.424 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (6 ml). Crystallization from isopropanol and diethylether yields 5-[8-methoxy-4-phenylamino-quinazolin-2-ylamino)-naphthalene-1-sulfonic acid methylamide hydrochloride, m.p. 272 - 274°C.

Example 70: 8-Methoxy-2-[4-(piperidin-1-yl)-phenylamino]-4-phenylamino-quinazoline dihydrochloride

A mixture of 2-chloro-8-methoxy-4-phenylamino-quinazoline (0.2 g) and N-(4-aminophenyl)-piperidine (0.164 g) is heated for 2 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in dioxane (1 ml) is added. Recrystallization from ethanol and diethylether yields 8-methoxy-2-[4-(piperidin-1-yl)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, Rf (A1) 0.47.

Example 71: 8-Methoxy-2-(4-methoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-8-methoxy-4-phenylamino-quinazoline (1.20 g) and 4-methoxy-aniline (0.66 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (15 ml). 4N HCl in dioxane (0.2 ml) is added. Crystallization from isopropanol and diethylether yields 8-methoxy-2-(4-methoxy-phenylamino)-4-phenylamino-quinazoline dihydrochloride, m.p. 287 - 289°C.

Example 72: 2-(4-Aminomethyl-phenylamino)-8-methoxy-4-phenylamino-quinazoline hydrochloride

A solution of 2-(4-cyano-phenylamino)-8-methoxy-4-phenylamino-quinazoline hydrochloride (1.10 g) in ethanol (50 ml) is hydrogenated in the presence of Raney nickel (0.5 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated in vacuo. The residue is dissolved in methanol. Addition of diethylether yields amorphous 2-(4-aminomethyl-phenylamino)-8-methoxy-4-phenylamino-quinazoline hydrochloride, Rf(E1) 0.24.

The starting material can be prepared, for example, as follows:

a) 2-(4-Cyano-phenylamino)-8-methoxy-4-phenylamino-quinazoline hydrochloride
A mixture of 2-chloro-8-methoxy-4-phenylamino-quinazoline (0.90 g) and

4-aminobenzonitrile (0.49 g) is heated for 3 min to produce a melt which is dissolved in isopropanol. 4N HCl in dioxane (1.0 ml) is added. Crystallization from isopropanol and diethylether yields 2-(4-cyano-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 307 - 308°C.

b) 2-Chloro-8-methoxy-4-phenylamino-quinazoline

A solution of 2,4-dichloro-8-methoxy-quinazoline (0.60 g), diisopropyl-ethylamine (0.87 ml),and aniline (0.26 ml) in isopropanol (10 ml) is heated to reflux for 45 min. The cold reaction mixture is filtered and residue is crystallized from dichloromethane and hexanes to give 2-chloro-8-methoxy-4-phenylamino-quinazoline, m.p. 245 - 246°C.

c) 2,4-Dichloro-8-methoxy-quinazoline

N,N-Dimethylaniline (0.36 ml) is added slowly to a solution of 8-methoxy-1H,3H-quinazolin-2,4-dione (*J. Chem. Soc.* **1921**,1425) (1.20 g) in phosphorousoxychloride (3.70 ml) while this mixture is heated up to 125°C. After the completion of the addition refluxing is continued for 10 h . Evaporation of the solvent in vacuo gives a residue which is added to ice and water. Extraction with ethylacetate yields 2,4-dichloro-8-methoxy-quinazoline, Rf(C4) 0.64.

Example 73: Naphthalene-1-sulfonic acid 4-[(4-amino-quinazolin-2-ylamino)-methyl]-benzylamide hydrochloride

A suspension of 0.165 g of 2-chloro-4-amino-quinazoline and 0.3 g of naphthalene-1-sulfonic acid 4-aminomethyl-benzylamide in 16 ml of isopentylalcohol is heated up to 100 °C for 15 hours. The resulting solution is concentrated and chromatographed on silica gel (A1) to give the product as a tan powder. This material is taken up in 7 ml of dichloromethane and treated at 0 °C with 3.5 ml of a 4 N HCl solution in dioxane. Concentration *in vacuo* provides a foam which is triturated in diethylether. The solids are collected and dried to yield naphthalene-1-sulfonic acid 4-[(4-amino-quinazolin-2-ylamino)-methyl]-benzylamide hydrochloride, melting at 215-224 °C. Rf (A1) 0.35; FAB-MS: $(M+H)^+$ = 470.

The starting material can be prepared, for example, as follows:

a) {4-[(Naphthalene-1-sulfonylamino)-methyl]-benzyl}-carbamic acid *tert*-butyl ester
A solution of 3 g of naphthalene-1-sulfonylchloride and 4.53 ml of N,N-diisopropyl-ethylamine in acetonitrile (80 ml) is cooled to 0 °C and treated with a solution of 3.12 g of (4-amino methyl-benzyl)-carbamic acid *tert*-butyl ester (*J. Med. Chem.* **1989**, *32*, 391-396) in acetonitrile (20 ml). The reaction mixture is stirred at ambient temperature for 30 min and concentrated. The residue is partitioned between dichloromethane and water. The organic phase is dried over magnesium sulfate and concentrated to a tan powder. Chromatography on silica gel (C3 then C2) affords {4-[(naphthalene-1-sulfonylamino)-methyl]-benzyl}-carbamic acid *tert*-butyl ester melting at 147-149 °C. Rf(C3) 0.25.

b) Naphthalene-1-sulfonic acid 4-aminomethyl-benzylamide
A suspension of {4-[(naphthalene-1-sulfonylamino)-methyl]-benzyl}-carbamic acid *tert*-butyl ester (5.25 g) in dichloromethane (33 ml) is treated with a 4 N HCl solution in dioxane (33 ml) at 0 °C. Under completion, the reaction mixture is concentrated *in vacuo*, the residue is partitioned between a 1 N aqueous NaOH solution and dichloromethane. After extraction with dichloromethane, the organics are dried over magnesium sulfate and concentrated to yield naphthalene-1-sulfonic acid 4-aminomethyl-benzylamide as a white foam. Rf(C4) 0.42.

Example 74: Naphthalene-1-sulfonic acid 3-[(4-amino-quinazolin-2-ylamino)-methyl]-benzylamide hydrochloride

In a procedure analogous to that of Example 73, a mixture of 0.264 g 2-chloro-4-amino-quinazoline and 0.48 g of naphthalene-1-sulfonic acid 3-aminomethyl-benzylamide is converted to naphthalene-1-sulfonic acid 3-[(4-amino-quinazolin-2-ylamino)-methyl]-benzylamide hydrochloride melting at 142-149 °C. Rf(A1) 0.33; FAB-MS: $(M+H)^+ = 470$.

The starting material can be prepared, for example, as follows:

a) {3-[(Naphthalene-1-sulfonylamino)-methyl]-benzyl}-carbamic acid *tert*-butyl ester
In a procedure analogous to that of Example 73a, a mixture of 3.12 g of (3-amino methyl-benzyl)-carbamic acid *tert*-butyl ester (*J. Med. Chem.* **1989**, *32*, 391-396) and 3 g of

naphthalene-1-sulfonylchloride in acetonitrile gives {3-[(naphthalene-1-sulfonylamino)-methyl]-benzyl}-carbamic acid *tert*-butyl ester melting at 104-105 °C. Rf(C3) 0.41.

b) Naphthalene-1-sulfonic acid 3-aminomethyl-benzylamide

Following the procedure described in Example 73b, {3-[(naphthalene-1-sulfonylamino)-methyl]-benzyl}-carbamic acid *tert*-butyl ester (4.97 g) is converted to naphthalene-1-sulfonic acid 3-aminomethyl-benzylamide as a foam. Rf(A3) 0.50.

Example 75: In a manner analogous to that described hereinbefore it is also possible to manufacture the following compounds:

2-(N-Methyl-4-methoxy-phenylamino)-8-methoxy-4-(4-cyano-phenylamino)-quinazoline

2-[N^1-Methyl-4-(acetaminomethyl)-phenylamino]-8-methoxy-4-(4-cyano-phenylamino)-quinazoline

2-[N^1-Methyl-4-(pyrolidin-1-yl-methyl)-phenylamino]-4-phenylamino-quinazoline

2-[N^1-Methyl-4-(pyrolidin-1-yl-methyl)-phenylamino]-8-methoxy-4-(4-cyano-phenylamino)-quinazoline

4-(4-Chloro-phenylamino)-2-[(4-pyrrolidin-1-yl-methyl)-phenylamino]-8-(2-hydroxy-ethoxy)-quinazoline

1-{4-[4-(4-Chloro-phenylamino)-8-(2-hydroxy-ethoxy)-quinazolin-2-ylamino]-benzyl}-2-pyrrolidin-2-on

2-(2-Chloro-4-methoxy-phenylamino)-8-(2-morpholino-ethoxy)-4-(2-methyl-phenylamino)-quinazoline

2-(2-Chloro-4-methoxy-phenylamino)-4-(2-methyl-phenylamino)-8-methoxy-quinazoline

2-(2-Methyl-4-methoxy-phenylamino)-4-(2-methyl-phenylamino)-8-methoxy-quinazoline

2-(2-Methyl-4-methoxy-phenylamino)-8-(2-morpholino-ethoxy)-4-(2-methyl-phenylamino)-quinazoline

4-(4-Chloro-phenylamino)-2-{4-[(cyclopropylmethyl-methylamino)-methyl]-2-methyl-phenylamino}-8-methoxy-quinazoline

2-[4-(Acetylamino-methyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline

2-[4-(Acetylamino-methyl)-phenylamino]-8-methoxy-4-(4-methoxy-phenylamino)-quinazoline

{3-[4-(4-Chloro-phenylamino)-8-ethyl-quinazolin-2-ylamino]-benzyl}-benzamide

2-[3-(Acetylamino-methyl)-phenylamino]-8-methoxy-4-(3-methoxy-phenylamino)-quinazoline

2-[4-(N-Piperidinyl-methyl)-phenylamino]-8-methoxy-4-(4-methoxy-phenylamino)-quinazoline

2-{3-[4-(4-Chloro-phenylamino)-8-(2-methoxy-ethoxy)-quinazolin-2-ylamino]-phenoxy}-N,N-dimethyl-acetamide

4-{4-[4-(4-Chloro-phenylamino)-8-(2-hydroxy-ethoxy)-quinazolin-2-ylamino]-phenyl}-1,1,1-trifluoro-butan-2-one

4-(4-Chloro-phenylamino)-8-methoxy-2-[4-(propane-2-sulfonylmethyl)-phenylamino]-quinazoline

6-N,N-Dimethylamino-4-(4-chloro-phenylamino)-2-[2-methoxymethyl-4-(propane-2-sulfonylmethyl)-phenylamino]-quinazoline

2-[2-Methoxymethyl-4-(propane-2-sulfonylmethyl)-phenylamino]-8-methyl-4-phenylamino-quinazoline

[4-(6-Chloro-4-phenylamino-quinazolin-2-ylamino)-3-methoxymethyl-phenyl]-N,N-dimethyl-methanesulfonamide

{4-[4-(4-Fluoro-phenylamino)-8-(2-hydroxy-ethoxy)-quinazolin-2-ylamino]-phenyl}-N,N-dimethyl-methanesulfonamide

{3-[4-(4-Fluoro-phenylamino)-8-methyl-quinazolin-2-ylamino]-phenyl}-N,N-dimethyl-methanesulfonamide

2-{4-[8-(2-Dimethylamino-ethoxy)-4-(4-fluoro-phenylamino)-quinazolin-2-ylamino]-phenyl}-ethanesulfonic acid dimethylamide

4-(4-Chloro-phenylamino)-2-[2-methoxy-4-(propane-2-sulfonylmethyl)-benzylamino]-6-methyl-quinazoline.

Example 76: N-Methyl-[4-(8-methyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methane-sulfonamide hydrochloride

In a procedure analogous to that of Example 44 2-chloro-8-methyl-4-phenylamino-quinazoline (0.254 g) and N-methyl-(4-aminophenyl)-methanesulfonamide (0.200 g) are reacted together to give N-methyl-[4-(8-methyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as light yellow crystals melting at 307-312°C.

The starting material can be prepared, for example, as follows:

2-Chloro-8-methyl-4-phenylamino-quinazoline

In a procedure analogous to that of Example 60 2,4-dichloro-8-methyl-quinazoline (1.09 g) (prepared as described in *Berichte* **1907**, *40*, 4414), aniline (0.57 g) and N,N-diisopropyl-

ethylamine (1.31 g) are reacted together to give 2-chloro-8-methyl-4-phenylamino-quinazoline as light yellow crystals melting at 133 - 135°C; Rf (B2) 0.36.

Example 76: N,N-Dimethyl-[4-(8-methyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride

In a procedure analogous to that of Example 44 2-chloro-8-methyl-4-phenylamino-quinazoline (0.211 g) and N,N-dimethyl-(4-aminophenyl)-methanesulfonamide (0.184 g) are reacted together to give N,N-dimethyl-[4-(8-methyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as light yellow crystals melting at 271 - 275°C.

Example 77: N,N-Dimethyl-[4-(8-methyl-4-methylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride

In a procedure analogous to that of Example 44 2-chloro-8-methyl-4-methylamino-quinazoline (0.17 g) and N,N-dimethyl-(4-aminophenyl)-methanesulfonamide (0.179 g) are reacted together to give N,N-dimethyl-[4-(8-methyl-4-methylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as light yellow crystals melting at 286 - 290°C; Rf (A1) 0.35.

The starting material can be prepared, for example, as follows:

2-Cloro-8-methyl-4-methylamino-quinazoline

A solution of 2,4-dichloro-8-methyl-quinazoline (0.336 g) (prepared as described in *Berichte* **1907**, *40*, 4414) and 5 ml of a 33 % solution of methylamine in ethanol is heated to 80°C for 30 min. in a sealed tube. After evaporation the residue is triturated with water, filtered and dried to give 2-chloro-8-methyl-4-methylamino-quinazoline as colorless crystals melting at 171 - 173°C; Rf (A2) 0.64.

Example 78: N,N-Dimethyl-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride

In a procedure analogous to that of Example 44 2-chloro-8-methoxy-4-phenylamino-quinazoline (0.4 g) (Example 66) and N,N-dimethyl-(4-aminophenyl)-methanesulfonamide (0.329 g) are reacted together to give N,N-dimethyl-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as light yellow crystals melting at 278 - 281°C; Rf (A1) 0.52.

Example 79: N(6),N(6)-Dimethyl-N(2),N(4)-diphenyl-quinazoline-2,4,6-triamine hydro-chloride

In a procedure analogous to that of Example 44 (2,4-dichloro-quinazolin-6-yl)-dimethylamine (0.13 g) and aniline (0.11 g) are reacted together to give N(6),N(6)-dimethyl-N(2),N(4)-diphenyl-quinazoline-2,4,6-triamine hydrochloride as yellow crystals melting at 281 - 286°C; Rf (A2) 0.21.

The starting material can be prepared, for example, as follows:

a) 2-Amino-5-dimethylamino-benzoic acid

A solution of 5-dimethylamino-2-nitro-benzoic acid (10 g) (prepared as described in *J. Med. Chem.* **1981**, *24*, 742) in methanol (300 ml) is hydrogenated in the presence of palladium on charcoal 10 % (0.5 g) at atmospheric pressure. The catalyst is removed by filtration through Celite after addition of 2N NaOH (5 ml). The filtrate neutralized with 2N HCl and the precipitate is collected, washed with methanol and dried to yield 2-amino-5-dimethylamino-benzoic acid as brown crystals melting at 224 - 228°C.

b) 6-Dimethylamino-quinazolin-2,4-dione

In a procedure analogous to that of Example 58b 2-amino-5-dimethylamino-benzoic acid (5.0 g) and potassium cyanate are reacted to give 6-dimethylamino-quinazolin-2,4-dione as yellow crystals melting at 326 - 329°C.

c) (2,4-Dichloro-quinazolin-6-yl)-dimethylamine

To a suspension of 6-dimethyl-quinazolin-2,4-dione (14.5 g) and N,N-dimethylaniline (15.5 g) is added slowly phosphorousoxychloride (66.7 g) and the reaction mixture is heated at reflux for 6 h. The reaction mixture is diluted with toluene (200 ml), poured into ice-water and the product is extracted with toluene. The organic extracts are washed with water, dried

and evaporated. The residue is crystallized from toluene to yield (2,4-dichloro-quinazolin-6-yl)-dimethylamine, m.p. 174 - 176°C; Rf (A2) 0.90.

Example 80: N(4)-(3-Chlorophenyl)-N(6),N(6)-dimethyl-N(2)-phenyl-quinazoline-2,4,6-triamine hydrochloride

In a procedure analogous to that of Example 44 2-chloro-N(4)-(3-chlorophenyl)-N(6),N(6)-dimethyl-quinazoline-4,6-diamine (0.092 g) and aniline (0.03 g) are reacted together to give N(4)-(3-chlorophenyl)-N(6),N(6)-dimethyl-N(2)-phenyl-quinazoline-2,4,6-triamine hydrochloride as yellow crystals melting at 299 - 303°C; Rf (A2) 0.26.

The starting material can be prepared, for example, as follows:

2-Chloro-N(4)-(3-chlorophenyl)-N(6),N(6)-dimethyl-quinazoline-4,6-diamine
In a procedure analogous to that of Example 60 (2,4-dichloro-quinazolin-6-yl)-dimethylamine (2 g), 3-chloraniline (1.57 g), N,N-diisopropyl-ethylamine (2.13 g) are reacted together to give 2-chloro-N(4)-(3-chlorophenyl)-N(6),N(6)-dimethyl-quinazoline-4,6-diamine as yellow crystals melting at 199 - 201°C; Rf (A2) 0.70.

Example 81: [4-(6-Dimethylamino-4-phenylamino-quinazolin-2-ylamino)-phenyl]-N,N-dimethyl-methanesulfonamide hydrochloride

In a procedure analogous to that of Example 44 2-chloro-N(6),N(6)-dimethylamino-N(4)-phenyl-quinazoline-4,6-diamine (0.105 g) and N,N-dimethyl-(4-aminophenyl)-methanesulfonamide (0.085 g) are reacted together to give [4-(6-dimethylamino-4-phenylamino-quinazolin-2-ylamino)-phenyl]-N,N-dimethyl-methanesulfonamide hydrochloride as light yellow crystals melting at 265 - 270°C; Rf (A2) 0.17.

The starting material can be prepared, for example, as follows:

2-Chloro-N(6),N(6)-dimethylamino-N(4)-phenyl-quinazoline-4,6-diamine
In a procedure analogous to that of Example 60 (2,4-dichloro-quinazolin-6-yl)-dimethylamine (2 g), aniline (1.15 g), N,N-diisopropyl-ethylamine (5 ml) are reacted together

to give 2-chloro-N(6),N(6)-dimethylamino-N(4)-phenyl-quinazoline-4,6-diamine as yellow crystals melting at 174 - 176°C; Rf (A2) 0.90.

Example 82: [4-(8-Dimethylaminomethyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-N,N-dimethyl-methanesulfonamide hydrochloride

In a procedure analogous to that of Example 44 (2-chloro-8-dimethylaminomethyl-quinazolin-4-yl)-phenyl-amine (0.03 g) and N-methyl-(4-aminophenyl)-methanesulfonamide (0.033 g) are reacted together to give [4-(8-dimethylaminomethyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-N,N-dimethyl-methanesulfonamide hydrochloride as light yellow powder; Rf (A1) 0.04.

The starting material can be prepared, for example, as follows:

a) 8-Bromomethyl-2,4-dichloro-quinazoline

A solution of 2,4-dichloro-8-methyl-quinazoline (35.5 g) (prepared as described in *Berichte* **1907**, *40*, 4414), N-bromosuccinimide (35.2 g) and dibenzoylperoxide (0.5 g) in carbon tetrachloride (900 ml) is heated at reflux for 2 h. The reaction mixture is filtered and the filtrate is washed with 0.5 N HCl and aqueous sodium thiosulfate solution. The organic extracts are dried over magnesium sulfate and concentrated. The crude product is recrystallized from isopropanol to give 8-bromomethyl-2,4-dichloro-quinazoline as light yellow needles melting at 160 - 162°C; Rf (B3) 0.19; Rf (B4) 0.43.

b) 8-Bromomethyl-2-chloro-4-phenylamino-quinazoline

A solution of 8-bromomethyl-2,4-dichloro-quinazoline (0.552 g), aniline hydrochloride (0.486 g), N,N-diisopropyl-ethylamine (0.64 ml), and N,N-dimethylformamide (10 ml) are reacted together at 25°C for 30 min. The reaction mixture is partitioned between toluene and water. The organic extracts are washed with 0.1 N aqueous HCl solution and brine, dried over magnesium sulfate and concentrated. Chromatography on silica gel (toluene) and recrystallization from dichloromethane and hexane yields 8-bromomethyl-2-chloro-4-phenyl-amino-quinazoline as light yellow crystals melting at 154 - 155°C; Rf (B4) 0.10.

c) (2-Chloro-8-dimethylaminomethyl-quinazolin-4-yl)-phenyl-amine

A solution of 8-bromomethyl-2-chloro-4-phenylamino-quinazoline (0.12 g), 0.35 ml of a solution of 8 % dimethylamine in toluene, and N,N-diisopropyl-ethylamine (0.12 ml) are reacted together at 25°C for 3 h. The reaction mixture is partitioned between ethyl acetate and 10 % aqueous sodium carbonate solution. The organic extracts are washed with brine, dried over magnesium sulfate and concentrated. Recrystallization from dichloromethane and hexane gives (2-chloro-8-dimethylaminomethyl-quinazolin-4-yl)-phenyl-amine as light yellow crystals melting at 195 - 197°C; Rf (A2) 0.05.

Example 83: 8-Methoxymethyl-N(2)-(4-methoxy-phenyl)-N(4)-phenyl-quinazoline-2,4-diamine hydrochloride

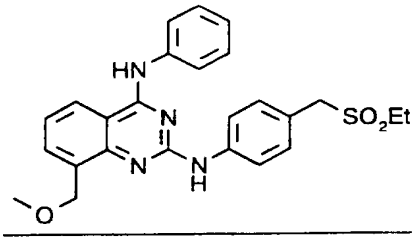
In a procedure analogous to that of Example 44 (2-chloro-8-methoxymethyl-quinazolin-4-yl)-phenyl-amine (0.09 g) and p-anisidine (0.044 g) are reacted together to give 8-methoxymethyl-N(2)-(4-methoxy-phenyl)-N(4)-phenyl-quinazoline-2,4-diamine hydrochloride as light yellow crystals melting at 252 - 256°C; Rf (A2) 0.48.

The starting material can be prepared, for example, as follows:

(2-Chloro-8-methoxymethyl-quinazolin-4-yl)-phenyl-amine

To a solution of 8-bromomethyl-2-chloro-4-phenylamino-quinazoline (0.345 g in methanol (30 ml) is added at 40°C a solution of 3 % sodium methylate in methanol (3.74 ml) and the reaction mixture is stirred for 30 min at this temperature. Under completion, the reaction mixture is concentrated *in vacuo*, the residue is partitioned between ethyl acetate and water. The organic extracts are washed with brine, dried over magnesium sulfate and concentrated. Chromatography on silica gel (toluene) and recrystallization from diethylether and hexane yields (2-chloro-8-methoxymethyl-quinazolin-4-yl)-phenyl-amine as light yellow crystals melting at 143 - 144°C; Rf (B2) 0.20.

Example 84: N(2)-(4-Ethanesulfonylmethyl-phenyl)-8-methoxymethyl-N(4)-phenyl-quinazoline-2,4-diamine hydrochloride



In a procedure analogous to that of Example 44 (2-chloro-8-methoxymethyl-quinazolin-4-yl)-phenyl-amine (0.205 g) and 4-ethanesulfonylmethyl-phenylamine (prepared as described in *I.G. Farbenind.* **1934**, 623 883) (0.156 g) are reacted together to give N(2)-(4-ethanesulfonylmethyl-phenyl)-8-methoxymethyl-N(4)-phenyl-quinazoline-2,4-diamine hydrochloride as yellow crystals melting at 266 - 271°C; Rf (A2) 0.60.

Example 85: [4-(8-Methoxymethyl-4-phenylamino-quinazolin-2-ylamino-phenyl]-N-methyl-methanesulfonamide hydrochloride

In a procedure analogous to that of Example 44 (2-chloro-8-methoxymethyl-quinazolin-4-yl)-phenyl-amine (0.181 g) and N-methyl-(4-aminophenyl)-methanesulfonamide (0.145 g) are reacted together to give [4-(8-methoxymethyl-4-phenylamino-quinazolin-2-ylamino-phenyl]-N-methyl-methanesulfonamide hydrochloride as yellow crystals melting at 257 - 262°C; Rf (A2) 0.42.

Example 86: N(2)-(4-Ethansulfonylmethyl-phenyl)-8-methoxy-N(4)-phenyl-quinazoline-2,4-diamine hydrochloride

In a procedure analogous to that of Example 44 (2-chloro-8-methoxy-quinazolin-4-yl)--phenyl-amine (example 66) (2.86 g) and 4-ethanesulfonylmethyl-phenylamine (prepared as described in *I.G. Farbenind.* **1934**, 623 883) (2.00 g) are reacted together to give N(2)-(4-ethansulfonylmethyl-phenyl)-8-methoxy-N(4)-phenyl-quinazoline-2,4-diamine hydrochloride as yellow crystals melting at >280°C; Rf (D3) 0.47.

Example 87: N(4)-Cyclopropyl-N(2)-(4-ethansulfonylmethyl-phenyl)-8-methoxy-quinazoline-2,4-diamine hydrochloride

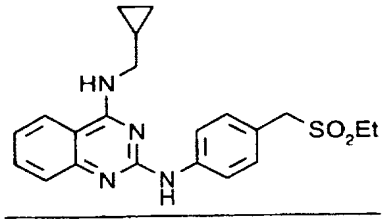
In a procedure analogous to that of Example 44 (2-chloro-8-methoxy-quinazolin-4-yl)--cyclopropyl-amine (0.375 g) and 4-ethanesulfonylmethyl-phenylamine (0.299 g) are reacted together to give N(4)-cyclopropyl-N(2)-(4-ethansulfonylmethyl-phenyl)-8-methoxy-quinazoline-2,4-diamine hydrochloride as colorless crystals melting at 268 - 270°C; Rf (D1) 0.40.

The starting material can be prepared, for example, as follows:

(2-Chloro-8-methoxy-quinazolin-4-yl)-cyclopropyl-amine

To a solution of 2,4-dichloro-quinazoline (10 g) (Example 1b) in isopropanol (200 ml) is added cyclopropylamine (4.51 g) at 0°C. The reaction mixture is stirred for 1.5 h at room temperature, concentrated *in vacuo*, and the residue is partitioned between chloroform and 0.1 N NaOH. The organic extracts are washed with brine, dried over magnesium sulfate and concentrated. Recrystallization from dichloromethane and hexane yields (2-chloro-8-methoxy-quinazolin-4-yl)-cyclopropyl-amine as white crystals melting at 189 - 191°C; Rf (A2) 0.50.

Example 88: N(4)-Cyclopropylmethylamino-N(2)-(4-ethansulfonylmethyl-phenylamino)-quinazoline hydrochloride



In a procedure analogous to that of Example 44 2-chloro-4-cyclopropylmethylamino--quinazoline (0.351 g) and 4-ethanesulfonylmethyl-phenylamine (0.299 g) are reacted together to give N(4)-cyclopropylmethylamino-N(2)-(4-ethansulfonylmethyl-phenylamino)-quinazoline hydrochloride as colorless crystals melting at > 280°C; Rf (D3) 0.45.

The starting material can be prepared, for example, as follows:

(2-Chloro-quinazolin-4-yl)-cyclopropylmethyl-amine

In a procedure analogous to that of Example 1a 2,4-dichloro-quinazoline (13 g), cyclopropylamine (5.9 ml), N,N-diisopropyl-ethylamine (13 ml) are reacted together to give (2-chloro-quinazolin-4-yl)-cyclopropylmethyl-amine as light yellow crystals melting at 154 - 155°C; Rf (B1) 0.48.

Example 90: N(2)-(4-Ethansulfonylmethyl-phenyl)-N(4)-methyl-quinazoline-2,4-diamine hydrochloride

In a procedure analogous to that of Example 44 (2-chloro-quinazolin-4-yl)-methyl-amine (0.291 g) and 4-ethanesulfonylmethyl-phenylamine (0.299 g) are reacted together to give N(2)-(4-ethansulfonylmethyl-phenyl)-N(4)-methyl-quinazoline-2,4-diamine hydrochloride as colorless crystals melting at > 280°C; Rf (D3) 0.41.

The starting material can be prepared, for example, as follows:

(2-Chloro-quinazolin-4-yl)-methyl-amine

In a procedure analogous to that of Example 1a 2,4-dichloro-quinazoline (15 g) and 8N methylylamine in ethanol (20.0 ml) are reacted together to give (2-chloro-quinazolin-4-yl)--methyl-amine as light yellow crystals melting at 212 - 213°C; Rf (B1) 0.33.

Example 91: N(4)-(2-Dimethylamino-ethyl)-N(2)-(4-ethanesulfonylmethyl-phenyl)-quinazoline-2,4-diamine hydrochloride

In a procedure analogous to that of Example 44 N-(2-chloro-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine (0.431 g) and 4-ethanesulfonylmethyl-phenylamine (0.299 g) are reacted together to give N(4)-(2-dimethylamino-ethyl)-N(2)-(4-ethanesulfonylmethyl-phenyl)-quinazoline-2,4-diamine hydrochloride as colorless crystals melting at > 240°C; Rf (D3) 0.21.

The starting material can be prepared, for example, as follows:

N-(2-Chloro-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine

In a procedure analogous to that of Example 1a 2,4-dichloro-quinazoline (5 g) and 2-dimethylamino-ethylamine (2.43 g) are reacted together to give N-(2-chloro-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine as white crystals melting at 64 - 67°C; Rf (A1) 0.30.

Example 92: {4-[4-(3-Chlorophenylamino)-quinazolin-2ylamino]-phenyl}-N,N-dimethyl-methanesulfonamide hydrochloride

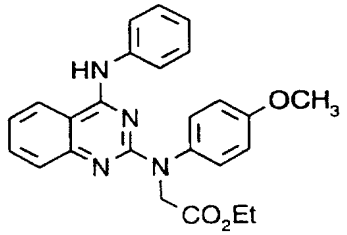
In a procedure analogous to that of Example 44 (3-chlorophenyl)-2-chloro-quinazolin-4-yl-amine (0.29 g) and N,N-dimethyl-(4-aminophenyl)-methanesulfonamide (0.214 g) are reacted together to give {4-[4-(3-chlorophenylamino)-quinazolin-2ylamino]-phenyl}-N,N-dimethyl-methanesulfonamide hydrochloride as colorless crystals melting at 239 - 242°C; Rf (D3) 0.48.

The starting material can be prepared, for example, as follows:

(3-Chlorophenyl)-2-chloro-quinazolin-4-yl-amine

In a procedure analogous to that of Example 1a 2,4-dichloro-quinazoline (8.4 g), 3-chloraniline (4.7 ml), N,N-diisopropyl-ethylamine (15 ml) are reacted together to give (3-chlorophenyl)-2-chloro-quinazolin-4-yl-amine as light yellow crystals melting at 197 - 199°C; Rf (D3) 0.50.

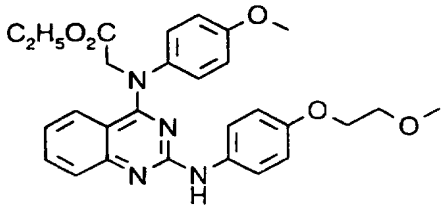
Example 93: [(4-Methoxyphenyl)-(4-phenylamino-quinazolin-2-yl)amino]-acetic acid ethyl ester



(2-Chloro-quinazolin-4-yl)-phenyl-amine (1 g) and N-(4-methoxyphenyl)-N-acetic acid ethyl ester (1.1 g) are heated up for 2 min to produce a melt. Isopropanol (2 mL) and water are added subsequently, the aqueous phase is adjusted to pH 11 and extracted with dichloromethane. The crude product is purified by flash chromatography on silica gel

(hexane/ethylacetate 6:1 to 4:1) to give a coloured oil which is recrystallized from a (1:3)-mixture of ethanol/hexane by adding methanol at room temperature. The title compound is obtained as a white crystalline powder, m.p. 93 - 95°C.

Example 94: [{2-[4-(2-methoxyethoxy)-phenylamino]-quinazolin-4-yl-(4-methoxyphenyl)-amino]-acetic acid ethyl ester



A mixture of [(2-chloro-quinazolin-4-yl-(4-methoxyphenyl)amino]-acetic acid ethyl ester (0.5 g) and 4-methoxyethoxy-aniline (0.292 g) is heated up for 1 min to produce a foaming melt. Isopropanol (1 ml), and water (10 ml) are subsequently added, the aqueous phase is adjusted to pH 11 and extracted with dichloromethane. The crude product is purified by flash chromatography on silica gel (hexane/ethylacetate 1:1) to give a yellow foam which is recrystallized from ethanol/hexane 4:1. The title compound is obtained as pale yellow solid, m.p. 126 - 128°C.

The starting material can be prepared, for example, as follows:

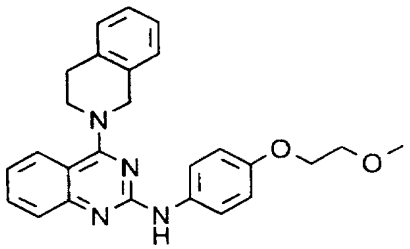
[(2-Chloro-quinazolin-4-yl-(4-methoxyphenyl)amino]-acetic acid ethyl ester

A suspension of 2,4-dichloro-quinazoline (4.5 g), N,N-diisopropyl-ethylamine (9.7 ml) and N-(4-methoxyphenyl)-N-acetic acid ethyl ester (6.15 g) in isopropanol (70 ml) is heated to 80 °C for 20 h. Volatiles are removed by evaporation at reduced pressure, and the residue is partitioned between water and ethylacetate. The combined organics are washed with brine, dried over magnesium sulfate and evaporated. The crude product is purified by flash cromatography on silica gel (hexane/ethylacetate 9:1 to 6:1) to give the title compound as an oil, Rf(C2) 0.33.

Example 95: N(4)-Cyclohexyl-N(4)-ethyl-N(2)-[4-(methoxyethoxy)-phenyl-quinazoline-2,4-diamine hydrochloride

A mixture of 2-chloro-4-[(N-cyclohexyl-N-ethyl)-amino]-quinazoline (0.3 g) and 4-methoxyethoxy-aniline (0.225 g) is heated for 1 min to produce a melt which is dissolved in isopropanol (1 ml). The mixture is evaporated, and the residue is partioned between dichloromethane (20 ml) and water. The aqueous phase is adjusted to pH 12 and extracted with methylenechloride, the combined organics are dried over magnesium sulfate and evaporated. The crude product is purified by flash chromatography on silica gel (hexane/ethylacetate 1:1) to give a foamy solid. The product is dissolved in dioxane (4 ml), 4N HCl in dioxane (0.268 ml) is added and the mixture is evaporated. The solid material is suspended in diethyl ether and filtered, followed by repeated washing with diethyl ether to yield N(4)-cyclohexyl-N(4)-ethyl-N(2)-[4-(methoxyethoxy)-phenyl-quinazoline-2,4-diamine hydrochloride as amorphous solid, Rf(A1) 0.48.

Example 96: [4-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-quinazolin-2-yl]-[4-(2-methoxyethoxy)phenyl]amine hydrochloride



A mixture of 2-chloro-4-(3,4-dihydro-1*H*-isoquinolin-2-yl)-quinazoline (0.3 g) and 4-methoxyethoxy-aniline (0.657 g) is heated for 1.5 min to produce a melt. Isopropanol (1 ml) and, after cooling, diethyl ether are added. The suspension is filtered, and the pale yellow solid is washed with a (1:1)-mixture of diethyl ether/isopropanol to give [4-(3,4-dihydro-1*H*-isoquinolin-2-yl)-quinazolin-2-yl]-[4-(2-methoxyethoxy)-phenyl]-amine hydrochloride, Rf(A2) 0.40.

The starting material can be prepared, for example, as follows:

a) 2-Chloro-4-(3,4-dihydro-1*H*-isoquinolin-2-yl)-quinazoline

A mixture of 2,4-dichloro-quinazoline (4.0 g), N,N-diisopropyl-ethylamine (10.3 ml) and 1,2,3,4-tetrahydroisoquinoline (2.69 ml) in isopentyl alcohol (40 ml) is heated to 150 °C for 2 h. Volatiles are removed by evaporation at reduced pressure, and the residue is partitioned

between a saturated sodium hydrogencarbonate solution and ethylacetate. The combined organics are dried over magnesium sulfate and evaporated. The crude product is purified by flash chromatography on silica gel (hexane/ethylacetate 9:1) to yield 2-chloro-4-(3,4-dihydro-1*H*-isoquinolin-2-yl)-quinazoline as a pale yellow oil which slowly crystallizes upon standing at room temperature, Rf (hexane/ethylacetate 6:1) 0.30.

In analogous manner as described hereinbefore, for example, following compounds can be prepared:

Example 97: 2-[4-(Benzoylamino-methyl)-phenylamino]-4-phenylamino-quinazoline hydrochloride
M.p. 228 - 229°C.

Example 98: 2-[4-(Amino-carbonyl)-phenylamino]-4-phenylamino-quinazoline hydrochloride
M.p. 334 - 337°C.

Example 99: 2-[4-(2-Hydroxy-ethyl)-phenylamino]-4-phenylamino-quinazoline hydrochloride
M.p. 288 - 291°C.

Example 100: 2-[4-(2-Hydroxy-ethyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride
M.p. 229 - 231°C.

Example 101: 2-[4-(2-Hydroxy-ethyl)-phenylamino]-8-methoxy-4-phenylamino-quinazoline hydrochloride
Rf(A1) 0.50.

Example 102: 2-[4-(2-Methoxy-ethyl)-phenylamino]-4-phenylamino-quinazoline hydrochloride
M.p. 234 - 236°C.

Example 103: 2-[4-(2-Methoxy-ethyl)-phenylamino]-4-(4-amino-carbonyl-phenylamino)-quinazoline hydrochloride

M.p. 288 - 290°C.

Example 104: 2-[4-(2-Methoxy-ethyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride
M.p. 218 - 220°C.

Example 105: 2-[4-(3-Hydroxy-propyl)-phenylamino]-8-methoxy-4-phenylamino-quinazoline hydrochloride
M.p. 250 - 252°C.

Example 106: 2-[4-(3-Hydroxy-propyl)-phenylamino]-4-phenylamino-quinazoline hydrochloride
M.p. 252 - 254°C.

Example 107: 2-[4-(3-Hydroxy-propyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride
M.p. 213 - 214°C.

Example 108: 2-[4-(3-Hydroxy-propyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride
M.p. 256 - 257°C.

Example 109: 2-[4-(2-Hydroxy-ethoxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride
M.p. 284 - 284°C.

Example 110: 2-[4-(2-Hydroxy-ethoxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride
M.p. 244 - 245°C.

Example 111: 2-[4-(2-Hydroxy-ethoxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride
M.p. 245 - 246°C.

Example 112: 2-[4-(2-Methoxy-ethyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride
M.p. 253 - 254°C.

Example 113: 2-[4-(3-Ethyl-4-methoxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride
M.p. 269 - 270°C.

Example 114: 2-[4-(3-Hydroxy-propyl)-phenylamino]-4-cyclohexylamino-quinazoline hydrochloride
M.p. 226 - 227°C.

Example 115: 4-(4-Chloro-phenylamino)-2-[4-(methoxy-acetylamino-methyl)-phenylamino]-8-methoxy-quinazoline hydrochloride
M.p. 265 - 266°C.

Example 116: 4-(4-Fluoro-phenylamino)-8-methoxy-2-[4-(2-hydroxyethyl)-phenylamino]-quinazoline hydrochloride
M.p. 235 - 237°C.

Example 117: 2-[4-(3-Hydroxy-propyl)-phenylamino]-4-(3-methyl-phenylamino)-quinazoline hydrochloride
M.p. 174 - 175°C.

Example 118: 2-[4-(3-Hydroxy-propyl)-phenylamino]-4-(3-hydroxyl-phenylamino)-quinazoline hydrochloride
M.p. 260 - 262°C.

Example 119: 6-Chloro-4-cyclohexylamino-2-[4-(3-hydroxy-propyl)-phenylamino]-quinazoline hydrochloride
M.p. 248 - 249°C.

Example 120: 6-Chloro-4-cyclohexylamino-2-[4-(2-hydroxy-ethoxy)-phenylamino]-quinazoline hydrochloride
M.p. 239 - 240°C.

Example 121: 2-[4-(3-Ethoxy-propoxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride
M.p. 200 - 202°C.

Example 122: 6-Fluoro-2-[4-(3-hydroxy-propyl)-phenylamino]-4-(3-methyl-phenylamino)-quinazoline hydrochloride
Rf(C4) 0.13

Example 123: 2-[4-(3-Benzyloxy-propoxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride
M.p. 177 - 180°C.

Example 124: 2-[4-(3-Benzyloxy-propoxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride
M.p. 138 - 140°C.

Example 125: 2-[4-(2-Methoxy-ethoxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride
M.p. 257 - 259°C.

Example 126: 4-Cyclohexylamino-2-[4-(3-benzyloxy-propoxy)-phenylamino]-quinazoline hydrochloride
M.p. 174 - 176°C.

Example 127: 2-[4-(2-Methoxy-ethoxy)-phenylamino]-4-(3-hydroxy-phenylamino)-quinazoline hydrochloride
M.p. 227 - 229°C.

Example 128: 2-[4-(2-Methoxy-ethoxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride

M.p. 204 - 205°C.

Example 129: 4-Cyclohexylamino-2-[4-(3-hydroxy-propoxy)-phenylamino]-quinazoline hydrochloride
M.p. 227 - 229°C.

Example 130: 4-Cyclohexylamino-2-(4-hydroxy-phenylamino)-quinazoline hydrochloride
M.p. 238 - 240°C.

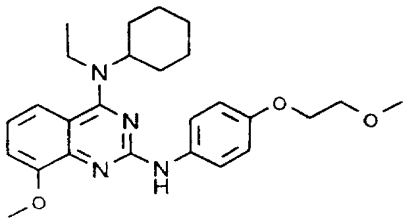
Example 131: 4-Cyclohexylamino-2-[4-(2-methoxy-ethoxy)-phenylamino]-8-methoxy-quinazoline hydrochloride
M.p. 247 - 248°C.

Example 132: 4-(4-Chloro-phenylamino)-2-[4-(2-methoxy-ethoxy)-phenylamino]-8-methoxy-quinazoline hydrochloride
M.p. 268 - 269°C.

Example 133: 4-(4-Fluoro-phenylamino)-2-[4-(2-methoxy-ethoxy)-phenylamino]-8-methoxy-quinazoline hydrochloride
M.p. 257 - 258°C.

Example 134: 4-Cyclohexylamino-2-[4-(2-methoxy-ethoxy)-phenylamino]-quinazoline hydrochloride
M.p. 188 - 190°C.

Example 135: 4-N-Ethyl-cyclohexylamino-2-[4-(2-methoxy-ethoxy)-phenylamino]-8-methoxy-quinazoline hydrochloride



M.p. 267 - 268°C.

Example 136: 4-(4-Chloro-phenylamino)-2-[4-(2-methoxyacetyl-aminomethyl)-phenylamino]-8-methoxy-quinazoline hydrochloride
M.p. 267 - 277°C.

Example 137: 4-Cyclohexylamino-8-methoxy-2-(4-phenylamino)-quinazoline hydrochloride
M.p. 292 - 293°C.

Example 138: 2,4-Di-(4-chloro-phenylamino)-quinazoline hydrochloride
M.p. 360 - 362°C.

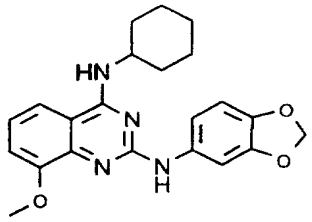
Example 139: 2-[4-(2-Methoxyacetyl-aminomethyl)-phenylamino]-8-methoxy-4-phenylamino-quinazoline hydrochloride
M.p. 255 - 256°C.

Example 140: 4-Cyclohexylamino-2-[4-(2-hydroxyethyl)-phenylamino]-quinazoline hydrochloride
M.p. 272 - 274°C.

Example 141: 2-[4-Aminomethyl)-phenylamino]-4-(4-chloro-phenylamino)-8-methoxy-quinazoline hydrochloride
Rf(dichloromethane - methanol-ammonia 40:10:1) 0.10.

Example 142: 2-[4-(3-Hydroxy-propoxy)-phenylamino]-4-(3-methyl-phenylamino)-quinazoline hydrochloride
M.p. 246 - 248°C.

Example 143: 4-Cyclohexylamino-2-[3,4-(methylene-dioxo)-phenylamino]-8-methoxy-quinazoline hydrochloride



M.p. 290 - 291°C.

Example 144: 2-[3,4-(Methylene-dioxo)-phenylamino]-8-methoxy-4-phenylamino-quinazoline hydrochloride
M.p. 267 - 269°C.

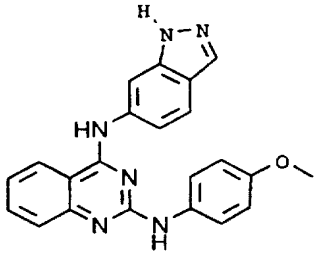
Example 145: 4-(4-Fluoro-phenylamino)-2-[3,4-(methylene-dioxo)-phenylamino]-8-methoxy-quinazoline hydrochloride
M.p. 296 - 297°C.

Example 146: 4-(3-Hydroxy-phenylamino)-2-[4-(piperidin-1-yl)-phenylamino]-quinazoline hydrochloride
Rf(A1) 0.31.

Example 147: 4-(3-Methyl-phenylamino)-2-[4-(3-benzyloxy-propoxy)-phenylamino]-quinazoline hydrochloride
M.p. 138 - 140°C.

Example 148: 2-[4-(2-Acetoxy-ethyl)-phenylamino]-4-phenylamino-quinazoline hydrochloride
M.p. 236 - 238°C.

Example 149: 4-[6-1(H)-Indazol-amino]-2-(4-methoxy-phenylamino)-quinazoline hydrochloride



M.p. 328 - 330°C.

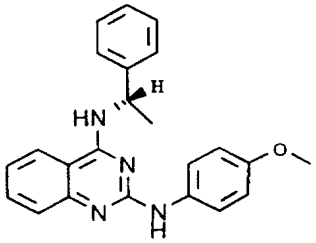
Example 150: 4-Cyclohexylamino-2-[4-(2-acetoxy-ethyl)-phenylamino]-quinazoline hydrochloride

M.p. 228 - 229°C.

Example 151: 4-Cyclohexylamino-2-[4-(3-pivaloyloxy-propoxy)-phenylamino]-quinazoline hydrochloride

M.p. 220 - 221°C.

Example 152: (S)-2-(4-Methoxy-phenylamino)-4-(1-phenyl-ethylamino)-quinazoline hydrochloride



M.p. 269 - 270°C.

Example 153: 4-(4-Chloro-phenylamino)-2-[(2-hydroxy-ethoxy)-phenylamino]-8-methoxy-quinazoline hydrochloride

M.p. 266 - 268°C.

Example 154: 8-Acetoxy-4-(4-chloro-phenylamino)-2-[(2-methoxy-ethoxy)-phenylamino]-quinazoline hydrochloride

Rf = 0.87 (dichloromethane - methanol 9:1).

Example 155: 4-Cyclohexylamino-2-(4-chloro-3-methoxy-phenylamino)-8-methoxy-quinazoline hydrochloride
Rf(A1) 0.50.

Example 156: 4-(4-Chloro-3-methoxy-phenylamino)-2-(4-methoxy-phenylamino)-quinazoline hydrochloride
M.p. 288 - 290°C.

Example 157: Tablets, each containing 50 mg of active ingredient, for example, 2,4-diphenylamino-quinazoline hydrochloride, can be prepared as follows:

Composition (for 10,000 tablets)

Active ingredient	500.0 g
Lactose	500.0 g
Potato starch	352.0 g
Gelatin	8.0 g
Talc	60.0 g
Magnesium stearate	10.0 g
Silica (highly disperse)	20.0 g
Ethanol	q.s.

The active ingredient is mixed with the lactose and 292 g of potato starch, and the mixture is moistened using an alcoholic solution of the gelatin and granulated by means of a sieve. After drying, the remainder of the potato starch, the talc, the magnesium stearate and the highly disperse silica are admixed and the mixture is compressed to give tablets of weight 145.0 mg each and active ingredient content 50.0 mg which, if desired, can be provided with breaking notches for finer adjustment of the dose.

Example 158: Coated tablets, each containing 100 mg of active ingredient, for example, 2,4-diphenylamino-quinazoline hydrochloride, can be prepared as follows:

Composition (for 1000 tablets):

Active ingredient	100.00 g
Lactose	100.00 g
Corn starch	70.00 g
Talc	8.50 g
Calcium stearate	1.50 g
Hydroxypropylmethylcellulose	2.36 g
Shellac	0.64 g
Water	q.s.
Dichloromethane	q.s.

The active ingredient, the lactose and 40 g of the corn starch are mixed and moistened and granulated with a paste prepared from 15 g of corn starch and water (with warming). The granules are dried, and the remainder of the corn starch, the talc and the calcium stearate are added and mixed with the granules. The mixture is compressed to give tablets (weight: 280 mg) and these are coated with a solution of the hydroxypropylmethylcellulose and the shellac in dichloromethane (final weight of the coated tablet: 283 mg).

Example 159: Tablets and coated tablets containing another compound of the formula (I) or a pharmaceutically acceptable salt of a compound of the formula (I), for example as in one of Examples 1 to 156 , can also be prepared in an analogous manner to that described in Examples 157 and 158.

SEQUENCE LISTING

(1) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1501 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 61..1432

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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TTAGTTTTGT TCTGAGAACG TTAGAGTTAT AGTACCGTGC GATCGTTCTT CAAGCTGCTA      60

ATG GAC GTC CTC TTC TTC CAC CAG GAT TCT AGT ATG GAG TTT AAG CTT      108
Met Asp Val Leu Phe Phe His Gln Asp Ser Ser Met Glu Phe Lys Leu
  1               5                  10                  15

GAG GAG CAT TTT AAC AAG ACA TTT GTC ACA GAG AAC AAT ACA GCT GCT      156
```

```
Glu Glu His Phe Asn Lys Thr Phe Val Thr Glu Asn Asn Thr Ala Ala
                20                  25                  30

GCT CGG AAT GCA GCC TTC CCT GCC TGG GAG GAC TAC AGA GGC AGC GTA      204
Ala Arg Asn Ala Ala Phe Pro Ala Trp Glu Asp Tyr Arg Gly Ser Val
        35                  40                  45

GAC GAT TTA CAA TAC TTT CTG ATT GGG CTC TAT ACA TTC GTA AGT CTT      252
Asp Asp Leu Gln Tyr Phe Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu
    50                  55                  60

CTT GGC TTT ATG GGC AAT CTA CTT ATT TTA ATG GCT GTT ATG AAA AAG      300
Leu Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala Val Met Lys Lys
65                  70                  75                  80

CGC AAT CAG AAG ACT ACA GTG AAC TTT CTC ATA GGC AAC CTG GCC TTC      348
Arg Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe
                85                  90                  95

TCC GAC ATC TTG GTC GTC CTG TTT TGC TCC CCT TTC ACC CTG ACC TCT      396
Ser Asp Ile Leu Val Val Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser
            100                 105                 110

GTC TTG TTG GAT CAG TGG ATG TTT GGC AAA GCC ATG TGC CAT ATC ATG      444
Val Leu Leu Asp Gln Trp Met Phe Gly Lys Ala Met Cys His Ile Met
        115                 120                 125

CCG TTC CTT CAA TGT GTG TCA GTT CTG GTT TCA ACT CTG ATT TTA ATA      492
Pro Phe Leu Gln Cys Val Ser Val Leu Val Ser Thr Leu Ile Leu Ile
    130                 135                 140

TCA ATT GCC ATT GTC AGG TAT CAT ATG ATA AAG CAC CCT ATT TCT AAC      540
Ser Ile Ala Ile Val Arg Tyr His Met Ile Lys His Pro Ile Ser Asn
145                 150                 155                 160

AAT TTA ACG GCA AAC CAT GGC TAC TTC CTG ATA GCT ACT GTC TGG ACA      588
Asn Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr
                165                 170                 175

CTG GGC TTT GCC ATC TGT TCT CCC CTC CCA GTG TTT CAC AGT CTT GTG      636
Leu Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val
            180                 185                 190
```

```
GAA CTT AAG GAG ACC TTT GGC TCA GCA CTG CTG AGT AGC AAA TAT CTC      684
Glu Leu Lys Glu Thr Phe Gly Ser Ala Leu Leu Ser Ser Lys Tyr Leu
        195                 200                 205

TGT GTT GAG TCA TGG CCC TCT GAT TCA TAC AGA ATT GCT TTC ACA ATC      732
Cys Val Glu Ser Trp Pro Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile
    210                 215                 220

TCT TTA TTG CTA GTG CAG TAT ATC CTG CCT CTA GTA TGT TTA ACG GTA      780
Ser Leu Leu Leu Val Gln Tyr Ile Leu Pro Leu Val Cys Leu Thr Val
225                 230                 235                 240

AGT CAT ACC AGC GTC TGC CGA AGC ATA AGC TGT GGA TTG TCC CAC AAA      828
Ser His Thr Ser Val Cys Arg Ser Ile Ser Cys Gly Leu Ser His Lys
                245                 250                 255

GAA AAC AGA CTC GAA GAA AAT GAG ATG ATC AAC TTA ACC CTA CAG CCA      876
Glu Asn Arg Leu Glu Glu Asn Glu Met Ile Asn Leu Thr Leu Gln Pro
            260                 265                 270

TCC AAA AAG AGC AGG AAC CAG GCA AAA ACC CCC AGC ACT CAA AAG TGG      924
Ser Lys Lys Ser Arg Asn Gln Ala Lys Thr Pro Ser Thr Gln Lys Trp
        275                 280                 285

AGC TAC TCA TTC ATC AGA AAG CAC AGA AGG AGG TAC AGC AAG AAG ACG      972
Ser Tyr Ser Phe Ile Arg Lys His Arg Arg Arg Tyr Ser Lys Lys Thr
    290                 295                 300
```

```
GCC TGT GTC TTA CCC GCC CCA GCA GGA CCT TCC CAG GGG AAG CAC CTA      1020
Ala Cys Val Leu Pro Ala Pro Ala Gly Pro Ser Gln Gly Lys His Leu
305                 310                 315                 320

GCC GTT CCA GAA AAT CCA GCC TCC GTC CGT AGC CAG CTG TCG CCA TCC      1068
Ala Val Pro Glu Asn Pro Ala Ser Val Arg Ser Gln Leu Ser Pro Ser
                325                 330                 335

AGT AAG GTC ATT CCA GGG GTC CCA ATC TGC TTT GAG GTG AAA CCT GAA      1116
Ser Lys Val Ile Pro Gly Val Pro Ile Cys Phe Glu Val Lys Pro Glu
            340                 345                 350

GAA AGC TCA GAT GCT CAT GAG ATG AGA GTC AAG CGT TCC ATC ACT AGA      1164
Glu Ser Ser Asp Ala His Glu Met Arg Val Lys Arg Ser Ile Thr Arg
        355                 360                 365

ATA AAA AAG AGA TCT CGA AGT GTT TTC TAC AGA CTG ACC ATA CTG ATA      1212
Ile Lys Lys Arg Ser Arg Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile
    370                 375                 380

CTC GTG TTC GCC GTT AGC TGG ATG CCA CTC CAC GTC TTC CAC GTG GTG      1260
Leu Val Phe Ala Val Ser Trp Met Pro Leu His Val Phe His Val Val
385                 390                 395                 400

ACT GAC TTC AAT GAT AAC TTG ATT TCC AAT AGG CAT TTC AAG CTG GTA      1308
Thr Asp Phe Asn Asp Asn Leu Ile Ser Asn Arg His Phe Lys Leu Val
                405                 410                 415

TAC TGC ATC TGT CAC TTG TTA GGC ATG ATG TCC TGT TGT CTA AAT CCG      1356
Tyr Cys Ile Cys His Leu Leu Gly Met Met Ser Cys Cys Leu Asn Pro
            420                 425                 430

ATC CTA TAT GGT TTC CTT AAT AAT GGT ATC AAA GCA GAC TTG AGA GCC      1404
Ile Leu Tyr Gly Phe Leu Asn Asn Gly Ile Lys Ala Asp Leu Arg Ala
        435                 440                 445

CTT ATC CAC TGC CTA CAC ATG TCA TGA TTCTCTCTGTG CACCAAAGAG          1452
Leu Ile His Cys Leu His Met Ser  *
    450                 455

AGAAGAAACG TGGTAATTGA CACATAATTT ATACAGAAGT ATTCTGGAT               1501
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 457 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Met Asp Val Leu Phe Phe His Gln Asp Ser Ser Met Glu Phe Lys Leu
 1               5                  10                  15

Glu Glu His Phe Asn Lys Thr Phe Val Thr Glu Asn Asn Thr Ala Ala
            20                  25                  30

Ala Arg Asn Ala Ala Phe Pro Ala Trp Glu Asp Tyr Arg Gly Ser Val
        35                  40                  45

Asp Asp Leu Gln Tyr Phe Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu
    50                  55                  60

Leu Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala Val Met Lys Lys
65                  70                  75                  80

Arg Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe
                85                  90                  95

Ser Asp Ile Leu Val Val Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser
            100                 105                 110

Val Leu Leu Asp Gln Trp Met Phe Gly Lys Ala Met Cys His Ile Met
        115                 120                 125

Pro Phe Leu Gln Cys Val Ser Val Leu Val Ser Thr Leu Ile Leu Ile
    130                 135                 140
```

Ser Ile Ala Ile Val Arg Tyr His Met Ile Lys His Pro Ile Ser Asn
145 150 155 160

Asn Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr
165 170 175

Leu Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val
180 185 190

Glu Leu Lys Glu Thr Phe Gly Ser Ala Leu Leu Ser Ser Lys Tyr Leu
195 200 205

Cys Val Glu Ser Trp Pro Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile
210 215 220

Ser Leu Leu Leu Val Gln Tyr Ile Leu Pro Leu Val Cys Leu Thr Val
225 230 235 240

Ser His Thr Ser Val Cys Arg Ser Ile Ser Cys Gly Leu Ser His Lys
245 250 255

Glu Asn Arg Leu Glu Glu Asn Glu Met Ile Asn Leu Thr Leu Gln Pro
260 265 270

Ser Lys Lys Ser Arg Asn Gln Ala Lys Thr Pro Ser Thr Gln Lys Trp
275 280 285

Ser Tyr Ser Phe Ile Arg Lys His Arg Arg Arg Tyr Ser Lys Lys Thr
290 295 300

Ala Cys Val Leu Pro Ala Pro Ala Gly Pro Ser Gln Gly Lys His Leu
305 310 315 320

Ala Val Pro Glu Asn Pro Ala Ser Val Arg Ser Gln Leu Ser Pro Ser
325 330 335

Ser Lys Val Ile Pro Gly Val Pro Ile Cys Phe Glu Val Lys Pro Glu
340 345 350

Glu Ser Ser Asp Ala His Glu Met Arg Val Lys Arg Ser Ile Thr Arg
355 360 365

```
Ile Lys Lys Arg Ser Arg Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile
    370                 375                 380

Leu Val Phe Ala Val Ser Trp Met Pro Leu His Val Phe His Val Val
385                 390                 395                 400

Thr Asp Phe Asn Asp Asn Leu Ile Ser Asn Arg His Phe Lys Leu Val
                405                 410                 415

Tyr Cys Ile Cys His Leu Leu Gly Met Met Ser Cys Cys Leu Asn Pro
            420                 425                 430

Ile Leu Tyr Gly Phe Leu Asn Asn Gly Ile Lys Ala Asp Leu Arg Ala
        435                 440                 445

Leu Ile His Cys Leu His Met Ser  *
    450                 455
```

(3) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1457 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 61..1432

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
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ATG TCT TTT TAT TCC AAG CAG GAC TAT AAT ATG GAT TTA GAG CTC GAC      108
Met Ser Phe Tyr Ser Lys Gln Asp Tyr Asn Met Asp Leu Glu Leu Asp
  1               5                  10                  15

GAG TAT TAT AAC AAG ACA CTT GCC ACA GAG AAT AAT ACT GCT GCC ACT      156
Glu Tyr Tyr Asn Lys Thr Leu Ala Thr Glu Asn Asn Thr Ala Ala Thr
             20                  25                  30

CGG AAT TCT GAT TTC CCA GTC TGG GAT GAC TAT AAA AGC AGT GTA GAT      204
Arg Asn Ser Asp Phe Pro Val Trp Asp Asp Tyr Lys Ser Ser Val Asp
         35                  40                  45

GAC TTA CAG TAT TTT CTG ATT GGG CTC TAT ACA TTT GTA AGT CTT CTT      252
Asp Leu Gln Tyr Phe Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu Leu
     50                  55                  60

GGC TTT ATG GGG AAT CTA CTT ATT TTA ATG GCT CTC ATG AAA AAG CGT      300
Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala Leu Met Lys Lys Arg
 65                  70                  75                  80

AAT CAG AAG ACT ACG GTA AAC TTC CTC ATA GGC AAT CTG GCC TTT TCT      348
Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe Ser
                 85                  90                  95

GAT ATC TTG GTT GTG CTG TTT TGC TCA CCT TTC ACA CTG ACG TCT GTC      396
Asp Ile Leu Val Val Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser Val
             100                 105                 110

TTG CTG GAT CAG TGG ATG TTT GGC AAA GTC ATG TGC CAT ATT ATG CCT      444
Leu Leu Asp Gln Trp Met Phe Gly Lys Val Met Cys His Ile Met Pro
         115                 120                 125

TTT CTT CAA TGT GTG TCA GTT TTG GTT TCA ACT TTA ATT TTA ATA TCA      492
Phe Leu Gln Cys Val Ser Val Leu Val Ser Thr Leu Ile Leu Ile Ser
     130                 135                 140
```

```
ATT GCC ATT GTC AGG TAT CAT ATG ATA AAA CAT CCC ATA TCT AAT AAT        540
Ile Ala Ile Val Arg Tyr His Met Ile Lys His Pro Ile Ser Asn Asn
145                 150                 155                 160

TTA ACA GCA AAC CAT GGC TAC TTT CTG ATA GCT ACT GTC TGG ACA CTA        588
Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr Leu
                165                 170                 175

GGT TTT GCC ATC TGT TCT CCC CTT CCA GTG TTT CAC AGT CTT GTG GAA        636
Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val Glu
            180                 185                 190

CTT CAA GAA ACA TTT GGT TCA GCA TTG CTG AGC AGC AGG TAT TTA TGT        684
Leu Gln Glu Thr Phe Gly Ser Ala Leu Leu Ser Ser Arg Tyr Leu Cys
        195                 200                 205

GTT GAG TCA TGG CCA TCT GAT TCA TAC AGA ATT GCC TTT ACT ATC TCT        732
Val Glu Ser Trp Pro Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile Ser
    210                 215                 220

TTA TTG CTA GTT CAG TAT ATT CTG CCC TTA GTT TGT CTT ACT GTA AGT        780
Leu Leu Leu Val Gln Tyr Ile Leu Pro Leu Val Cys Leu Thr Val Ser
225                 230                 235                 240

CAT ACA AGT GTC TGC AGA AGT ATA AGC TGT GGA TTG TCC AAC AAA GAA        828
His Thr Ser Val Cys Arg Ser Ile Ser Cys Gly Leu Ser Asn Lys Glu
                245                 250                 255

AAC AGA CTT GAA GAA AAT GAG ATG ATC AAC TTA ACT CTT CAT CCA TCC        876
Asn Arg Leu Glu Glu Asn Glu Met Ile Asn Leu Thr Leu His Pro Ser
            260                 265                 270

AAA AAG AGT GGG CCT CAG GTG AAA CTC TCT GGC AGC CAT AAA TGG AGT        924
Lys Lys Ser Gly Pro Gln Val Lys Leu Ser Gly Ser His Lys Trp Ser
        275                 280                 285

TAT TCA TTC ATC AAA AAA CAC AGA AGA AGA TAT AGC AAG AAG ACA GCA        972
Tyr Ser Phe Ile Lys Lys His Arg Arg Arg Tyr Ser Lys Lys Thr Ala
    290                 295                 300
```

```
TGT GTG TTA CCT GCT CCA GAA AGA CCT TCT CAA GAG AAC CAC TCC AGA      1020
Cys Val Leu Pro Ala Pro Glu Arg Pro Ser Gln Glu Asn His Ser Arg
305                 310                 315                 320

ATA CTT CCA GAA AAC TTT GGC TCT GTA AGA AGT CAG CTC TCT TCA TCC      1068
Ile Leu Pro Glu Asn Phe Gly Ser Val Arg Ser Gln Leu Ser Ser Ser
                325                 330                 335

AGT AAG TTC ATA CCA GGG GTC CCC ACT TGC TTT GAG ATA AAA CCT GAA      1116
Ser Lys Phe Ile Pro Gly Val Pro Thr Cys Phe Glu Ile Lys Pro Glu
            340                 345                 350

GAA AAT TCA GAT GTT CAT GAA TTG AGA GTA AAA CGT TCT GTT ACA AGA      1164
Glu Asn Ser Asp Val His Glu Leu Arg Val Lys Arg Ser Val Thr Arg
        355                 360                 365

ATA AAA AAG AGA TCT CGA AGT GTT TTC TAC AGA CTG ACC ATA CTG ATA      1212
Ile Lys Lys Arg Ser Arg Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile
    370                 375                 380

TTA GTA TTT GCT GTT AGT TGG ATG CCA CTA CAC CTT TTC CAT GTG GTA      1260
Leu Val Phe Ala Val Ser Trp Met Pro Leu His Leu Phe His Val Val
385                 390                 395                 400

ACT GAT TTT AAT GAC AAT CTT ATT TCA AAT AGG CAT TTC AAG TTG GTG      1308
Thr Asp Phe Asn Asp Asn Leu Ile Ser Asn Arg His Phe Lys Leu Val
                405                 410                 415

TAT TGC ATT TGT CAT TTG TTG GGC ATG ATG TCC TGT TGT CTT AAT CCA      1356
Tyr Cys Ile Cys His Leu Leu Gly Met Met Ser Cys Cys Leu Asn Pro
            420                 425                 430

ATT CTA TAT GGG TTT CTT AAT AAT GGG ATT AAA GCT GAT TTA GTG TCC      1404
Ile Leu Tyr Gly Phe Leu Asn Asn Gly Ile Lys Ala Asp Leu Val Ser
        435                 440                 445

CTT ATA CAC TGT CTT CAT ATG TAA TAA TTCTCACTGT TTACCAAGGA            1452
Leu Ile His Cys Leu His Met  *   *
    450                 455

AAGAAC                                                              1457
```

(4) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 457 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
Met Ser Phe Tyr Ser Lys Gln Asp Tyr Asn Met Asp Leu Glu Leu Asp
 1               5                  10                  15

Glu Tyr Tyr Asn Lys Thr Leu Ala Thr Glu Asn Asn Thr Ala Ala Thr
            20                  25                  30

Arg Asn Ser Asp Phe Pro Val Trp Asp Asp Tyr Lys Ser Ser Val Asp
        35                  40                  45

Asp Leu Gln Tyr Phe Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu Leu
    50                  55                  60

Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala Leu Met Lys Lys Arg
65                  70                  75                  80

Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe Ser
                85                  90                  95

Asp Ile Leu Val Val Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser Val
            100                 105                 110

Leu Leu Asp Gln Trp Met Phe Gly Lys Val Met Cys His Ile Met Pro
        115                 120                 125

Phe Leu Gln Cys Val Ser Val Leu Val Ser Thr Leu Ile Leu Ile Ser
    130                 135                 140

Ile Ala Ile Val Arg Tyr His Met Ile Lys His Pro Ile Ser Asn Asn
145                 150                 155                 160
```

Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr Leu
165 170 175

Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val Glu
180 185 190

Leu Gln Glu Thr Phe Gly Ser Ala Leu Leu Ser Ser Arg Tyr Leu Cys
195 200 205

Val Glu Ser Trp Pro Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile Ser
210 215 220

Leu Leu Leu Val Gln Tyr Ile Leu Pro Leu Val Cys Leu Thr Val Ser
225 230 235 240

His Thr Ser Val Cys Arg Ser Ile Ser Cys Gly Leu Ser Asn Lys Glu
245 250 255

Asn Arg Leu Glu Glu Asn Glu Met Ile Asn Leu Thr Leu His Pro Ser
260 265 270

Lys Lys Ser Gly Pro Gln Val Lys Leu Ser Gly Ser His Lys Trp Ser
275 280 285

Tyr Ser Phe Ile Lys Lys His Arg Arg Arg Tyr Ser Lys Lys Thr Ala
290 295 300

Cys Val Leu Pro Ala Pro Glu Arg Pro Ser Gln Glu Asn His Ser Arg
305 310 315 320

Ile Leu Pro Glu Asn Phe Gly Ser Val Arg Ser Gln Leu Ser Ser Ser
325 330 335

Ser Lys Phe Ile Pro Gly Val Pro Thr Cys Phe Glu Ile Lys Pro Glu
340 345 350

Glu Asn Ser Asp Val His Glu Leu Arg Val Lys Arg Ser Val Thr Arg
355 360 365

Ile Lys Lys Arg Ser Arg Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile
370 375 380

```
Leu Val Phe Ala Val Ser Trp Met Pro Leu His Leu Phe His Val Val
385                 390                 395                 400

Thr Asp Phe Asn Asp Asn Leu Ile Ser Asn Arg His Phe Lys Leu Val
                405                 410                 415

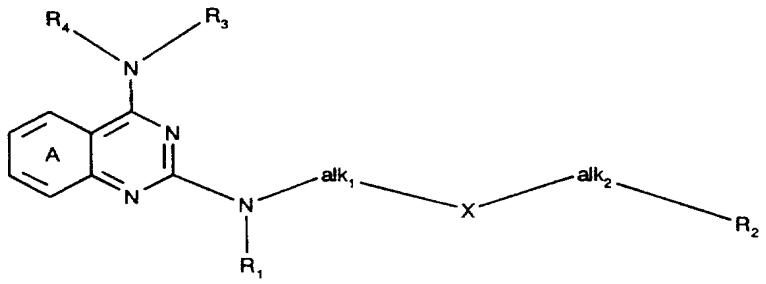
Tyr Cys Ile Cys His Leu Leu Gly Met Met Ser Cys Cys Leu Asn Pro
            420                 425                 430

Ile Leu Tyr Gly Phe Leu Asn Asn Gly Ile Lys Ala Asp Leu Val Ser
        435                 440                 445

Leu Ile His Cys Leu His Met  *   *
    450                 455
```

What is claimed is

1. Use of a compound of formula (I)



in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R_2 represents

(i) hydrogen, halogen, nitro, cyano, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, by lower alkoxy, by amino, by substituted amino, by carboxy, by lower alkoxycarbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl, by carbamoyl, or by N-substituted carbamoyl;

(ii) amino or substituted amino;

(iii) hydroxy, lower alkoxy, lower alkenyloxy, lower alkynyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C_3-C_8-cycloalkoxy, C_3-C_8-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl-oxy, aminocarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) carbamoyl or N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-O-R, -NR_1-CO-R, -NR_1-CO-NR_1-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-

substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula $-X_1(X_2)(X_3)$ wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula $-X_4-(CO)_p-(CH_2)_o-$, $-(CH_2)_q-X_4-(CO)_p-(CH_2)_r-$, or $-(CH_2)_s-X_4-CO-(CH_2)_t-$; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula $-CO-(CH_2)_u-$; [X_4 being $-CH_2-$, $-N(R_1)-$ or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from $-CH_2-$;];

R_3 and R_4 , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, N-substituted carbamoyl, and $-S(O)_n-R$;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents (carbocyclic or heterocyclic) arylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, lower alkynyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, (carbocyclic or heterocyclic) aroyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iv) amino, substituted amino;
(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen, lower alkyl, lower alkenyl, lower alkinyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO_2-R, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy;

wherein, in each case, R represents hydrogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy; or a pharmaceutically accetable salt thereof, for the manufacture of a pharmaceutical composition for treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype.

2. Use according to claim 1 for the manufacture of a pharmaceutical composition for treatment and prophylaxis of disorders or disease states caused by eating disorders, of obesity, bulimia nervosa, diabetes, dyspilipidimia, hypertension, memory loss, epileptic seizures, migraine, sleep disturbance, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion or diarrhea.

3. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R_2 represents

(i) hydrogen, halogen, nitro, cyano, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by lower alkoxy, by substituted amino, by lower alkoxycarbonyl, or by N-substituted carbamoyl;

(ii) substituted amino;

(iii) hydroxy, lower alkoxy, lower alkoxy-lower alkoxy, C_3-C_8-cyclo-alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-O-R, -NR_1-CO-R, -NR_1-CO-NR_1-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X_1(X_2)(X_3) wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula -X_4-$(CO)_p$-$(CH_2)_o$-, -$(CH_2)_q$-X_4-$(CO)_p$-$(CH_2)_r$-, or -$(CH_2)_s$-X_4-CO-$(CH_2)_t$-; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula -CO-$(CH_2)_u$-; [X_4 being -CH_2-, -N(R_1)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from -CH_2-;];

R_3 and R_4 , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, N-substituted carbamoyl, and -$S(O)_n$-R;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, or NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents phenylene, naphthylene, thiophenylene, furylene, or pyridylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived and selected from the group consisting of phenyl, biphenylyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl, pyridyl, indolyl, indazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinolinyl, isoquinolinyl, or quinazolinyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by $-CO-(O)_v-R$ and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

4. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 represents a single bond or C_1-C_3-alkylene;

alk_2 represents a single bond or C_1-C_3-alkylene;

R_1 represents hydrogen, lower alkyl or lower alkyl which is substituted by lower alkoxy-carbonyl;

R_2 represents

(i) hydrogen, halogen, cyano, nitro, lower alkyl, C_3-C_7-cycloalkyl, or phenyl;

(ii) amino, amino which is mono-substituted by lower alkyl, by lower alkoxy-lower alkyl, by phenyl, by pyridyl, or which is disubstituted by lower alkyl or by C_2-C_6-alkylene;

(iii) hydroxy, lower alkanoyloxy, or lower alkoxy which is unsubstituted or substituted by hydroxy, by lower alkoxy, by phenyl-lower alkoxy, by lower-alkanoyloxy, by C_3-C_8-cycloalkyl or by phenyl;

(iv) a group selected from $-NR_1-CO-R$, $-NR_1-SO_2-R$, $-SO_2-R$, or $-SO_2-NR_1-R$, [R being lower alkyl, lower alkoxy-lower alkyl, phenyl, or naphthyl, and the group $-N(R)(R_1)$ represents amino which is mono-substituted by lower alkyl or by lower alkoxy-lower alkyl, or which is di-substituted by lower alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or lower alkyl}];

(vi) carbamoyl;

R_3 represents hydrogen, lower alkyl which is unsubstituted or substituted by C_3-C_7-cycloalkyl, by phenyl, or by di-lower alkylamino, or represents C_3-C_7-cycloalkyl, phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, hydroxy, and carbamoyl, or represents indazolyl;

R_4 represents hydrogen or lower alkyl which is unsubstituted or substituted by lower alkoxy-carbonyl; or

R_3 and R_4 together represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, halo-lower alkyl, lower alkoxy, or oxy-lower alkylene-oxy, or represents nahthylene;

wherein the benzo ring A is unsubstituted or substituted a substituent selected from the group consisting of: halogen, nitro, amino, di-lower alkylamino, lower alkyl, lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower alkyl, di-(lower alkyl)-amino-lower alkyl, phenyl, and lower alkanoyl.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 represents a single bond;

alk_2 represents a single bond or C_1-C_3-alkylene;

R_1 represents hydrogen or lower alkyl;

R_2 represents

(i) hydrogen, halogen, cyano, nitro, lower alkyl, or phenyl;

(ii) amino which is mono-substituted by lower alkyl, phenyl or pyridyl, or which is disubstituted by lower alkyl or by C_2-C_6-alkylene;

(iii) hydroxy or lower alkoxy which is unsubstituted or substituted by C_3-C_8-cycloalkyl or by phenyl;

(iv) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, or -SO_2-NR_1-R, [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl, R_1 being as defined above, or the group -N(R)(R_1) represents amino which is mono-substituted by lower alkyl, by hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or lower alkyl}];

R_3 represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R_4 represents hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, halo-lower alkyl, lower alkoxy, lower alkoxy-lower alkyl;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of
halogen, lower alkyl, halo-lower alkyl, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

5. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

(a) alk_1 and alk_2 both represents a single bond; and

R_2 represents hydrogen, amino which is disubstituted by by C_2-C_6-alkylene, especially pentylene, or C_1-C_4-alkoxy, especially methoxy; or

(b) alk_1 represents a single bond; alk_2 represents C_1-C_3-alkylene; and

R_2 represents (iv) a group selected from -NH-SO_2-R , -SO_2-R, or -SO_2-NH-R, [R being C_1-C_4-alkyl, or naphthyl, or the group -NH(R) represents amino which is mono-substituted by C_1-C_4-alkyl, by hydroxy-C_1-C_4-alkyl, or by naphthyl, or which is di-substituted by C_1-C_4-alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or C_1-C_4-alkyl}];

and, in each case,

R_1 represents hydrogen;

R_3 represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, C_1-C_4-alkyl, C_1-C_4-alkoxy, and oxy- C_1-C_4-alkylene-oxy; and

R_4 represents hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, C_1-C_4-alkyl, or C_1-C_4-alkoxy;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy.

6. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

(a) alk_1 and alk_2 both represents a single bond; and

R_2 represents hydrogen, amino which is disubstituted by by C_2-C_6-alkylene, especially pentylene, or C_1-C_4-alkoxy, especially methoxy; or

(b) alk_1 represents a single bond; alk_2 represents C_1-C_3-alkylene; and

R_2 represents (iv) a group selected from -NH-SO_2-R , -SO_2-R, or -SO_2-NH-R, [R being C_1-C_4-alkyl, or naphthyl, or the group -NH(R) represents amino which is mono-substituted by C_1-C_4-alkyl, by hydroxy-C_1-C_4-alkyl, or by naphthyl, or which is di-substituted by C_1-C_4-alkyl or by C_2-C_6-alkylene {which may be interrupted by O or NR_0, R_0 being hydrogen or C_1-C_4-alkyl}];

and, in each case,

R_1 represents hydrogen;

R_3 represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, C_1-C_4-alkyl, C_1-C_4-alkoxy, and oxy- C_1-C_4-alkylene-oxy; and

R_4 represents hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, C_1-C_4-alkyl, or C_1-C_4-alkoxy;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy.

7. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 represents a single bond;

alk_2 represents a single bond or C_1- or C_2-alkylene;

R_1 represents hydrogen;

R_2 represents hydrogen, hydroxy, C_1-C_4-alkoxy, especially methoxy, lower alkoxy-lower alkoxy, phenyl-lower alkoxy-lower alkoxy, amino, amino which is disubstituted by by C_2-C_6-alkylene, especially pentylene, lower alkoxycarbonyl-amino, or -SO_2-R or -SO_2-NH-R and R being C_1-C_4-alkyl, especially methyl; and, in each case;

R_3 represents C_3-C_6-cycloalkyl, phenyl-lower alkyl, or phenyl which is unsubstituted or is substituted by halogen, hydroxy, or lower alkoxy;

R_4 represents hydrogen; and

X represents 1,4-phenylene or 1,3-phenylene which is di-substituted by oxy-methylene-oxy;

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

8. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk_1 and alk_2 both represent a single bond;

R_1 is hydrogen;

R_4 is hydrogen;

X is 1,4-phenylene;

R_2 is C_1-C_4-alkoxy, especially methoxy, and R_3 is phenyl which is substituted by hydroxy, especially 3-hydroxy-phenyl; or

R_2 is C_1-C_4-alkoxy-C_1-C_4-alkoxy, especially 2-methoxy-ethoxy, or 1-piperidino; and

R_3 is phenyl; and

the benzo ring A is unsubstituted or substituted in position 8 of the quinazoline ring by C_1-C_4-alkoxy, especially methoxy.

9. A compound of formula (I) or a salt thereof in which;

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R_2 represents a group selected from -CH(OH)-R, -CO-R, $-NR_1$-CO-O-R, $-NR_1$-CO-R, $-NR_1$-CO-NR_1-R, $-NR_1$-SO_2-R, $-NR_1$-SO_2-NR_1-R, $-SO_2$-R, $-SO_2$-NR_1-R, or $-SO_2$-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula $-X_1(X_2)(X_3)$ wherein, (a) if X_1 is -CH-, X_2 together with X_3 represent a structural element of formula $-X_4$-$(CO)_p$-$(CH_2)_o$-, $-(CH_2)_q$-X_4-$(CO)_p$-$(CH_2)_r$-, or $-(CH_2)_s$-X_4-CO-$(CH_2)_t$-; or, (b) if X_1 is -N-, X_2 together with X_3 represent a structural element of formula -CO-$(CH_2)_u$-; [X_4 being $-CH_2$-, -N(R_1)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from $-CH_2$-;];

R_3 and R_4 , independently of one another, represent
(i) hydrogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, N-substituted carbamoyl, and -$S(O)_n$-R;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents (carbocyclic or heterocyclic) arylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of
(i) halogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, lower alkynyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, (carbocyclic or heterocyclic) aroyl, nitro, cyano;
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
(iv) amino, substituted amino;
(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by $-CO-(O)_v-R$ and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen, lower alkyl, lower alkenyl, lower alkinyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, $-SO_2-R$, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy;

wherein, in each case, R represents hydrogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

10. A compound according to claim 9 of formula (I) or a salt thereof selected from the group consisting of

2,4-Diphenylamino-quinazoline,

2-(4-Methoxy-phenylamino)-4-phenylamino-quinazoline;

2-(4-Fluoro-phenylamino)-4-phenylamino-quinazoline;

2-(4-Phenyl-phenylamino)-4-phenylamino-quinazoline;

2-[4-(N,N-Dimethylamino)-phenylamino]-4-phenylamino-quinazoline;

2-(3,4-Dimethoxy-phenylamino)-4-phenylamino-quinazoline;

2-[4-(N,N-Diethylamino)-phenylamino]-4-phenylamino-quinazoline;

2-[4-(Benzyloxy)-phenylamino]-4-phenylamino-quinazoline;

2-(4-Amino-phenylamino)-4-phenylamino-quinazoline;

2-[3-(N,N-Dimethylamino)-phenylamino]-4-phenylamino-quinazoline;

2-[4-(N,N-Dipropylamino)-phenylamino]-4-phenylamino-quinazoline;

2-(4-Cyano-phenylamino)-4-phenylamino-quinazoline;

2-[4-(2-Pyridylamino)-phenylamino]-4-phenylamino-quinazoline;

2-[4-(Aminomethyl)-phenylamino]-4-phenylamino-quinazoline;

2-[3-(Aminomethyl)-phenylamino]-4-phenylamino-quinazoline;

2-(4-Hydroxy-phenylamino)-4-phenylamino-quinazoline;

2-[4-(3-Cyclohexyl-propyloxy)-phenylamino]-4-phenylamino-quinazoline;

2,4-Di-(4-methoxy-phenylamino)-quinazoline;

2-(4-Cyano-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline;

2-[4-(N,N-Diethylamino)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;

2-(4-Cyclohexyl-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline;

2-(4-Methoxy-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline;

2-[4-(Aminomethyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;

2-(4-N,N-Diethylamino-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline;

2-[4-(N,N-Dipropylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;

2-(4-Cyclohexyl-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline;

2-(4-Hydroxy-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline;

2-[4-(2-Pyridylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;

2-[4-(N,N-Dimethylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;

2-[4-(Piperidin-1-yl)-phenylamino]-4-phenylamino-quinazoline;

2-[4-(Benzyloxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;

2-(4-Hydroxy-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline;

2-[3-(N,N-Dimethylamino)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;

2-(4-Chloro-phenylamino)-4-phenylamino-quinazoline;

2-(4-Methyl-phenylamino)-4-phenylamino-quinazoline;

2-(3-Methoxy-phenylamino)-4-phenylamino-quinazoline;

2-(2-Methoxy-phenylamino)-4-phenylamino-quinazoline;

2-(4-Nitro-phenylamino)-4-phenylamino-quinazoline;

2,4-Di-(3-methoxy-phenylamino)-quinazoline;

2-[4-(Benzyloxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;

2-[4-(Aminomethyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;

2-[4-(Piperidin-1-yl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;

2-[4-(Piperidin-1-yl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;

N-Methyl-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide;

N-2-[4-(4-Methyl-piperidine-1-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine;

N-2-[4-(N-Methyl-piperazine-1-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine;

N-2-[4-(N-Methyl-piperazine-1-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine;
N-2-[4-(Morpholine-4-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine;
N,N-Dimethyl-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide;
N-(2-Methoxy-ethyl)-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide;
2-[4-(Ethanesulfonylmethyl)-phenylamino]-4-phenylamino-quinazoline;
N-{4-[4-(4-Methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl}-methanesulfonamide;
N-{4-[4-(4-Methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl}-methanesulfonamide;
N-{4-[4-(3-Methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl}-methanesulfonamide;
N-[4-(4-Phenylamino-quinazolin-2-ylamino)-benzyl]-methanesulfonamide;
6-Bromo-2,4-di-(3-methoxy-phenylamino)-quinazoline;
6-Bromo-2,4-di-(3-methoxy-phenylamino)-quinazoline;
2-(3-Methoxy-phenylamino)-6-nitro-4-phenylamino-quinazoline;
6-Amino-2-(3-methoxy-phenylamino)-4-phenylamino-quinazoline;
2,4-Diphenylamino-6-phenyl-quinazoline;
N,N-Dimethyl-[4-(6-phenyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methane-sulfonamide;
N,N-Dimethyl-[4-(5-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methane-sulfonamide;
N-Methyl-[4-(6-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide;
6-Methoxy-2-(4-methoxy-phenylamino)-4-phenylamino-quinazoline;
2-(4-Hydroxy-phenylamino)-6-methoxy-4-phenylamino-quinazoline;
2-(4-Benzyloxy-phenylamino)-6-methoxy-4-phenylamino-quinazoline;
N-Methyl-[4-(7-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide;
N-Methyl-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide;
N-[4-(8-Methoxy-4-phenylamino-quinazolin-2-ylamino)-benzyl]-methanesulfonamide;
N-{4-[8-Methoxy-4-(3-methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl]}-methanesulfonamide;
5-[8-Methoxy-4-phenylamino-quinazolin-2-ylamino)-naphthalene-1-sulfonic acid methylamide;
8-Methoxy-2-[4-(piperidin-1-yl)-phenylamino]-4-phenylamino-quinazoline;
8-Methoxy-2-(4-methoxy-phenylamino)-4-phenylamino-quinazoline;
2-(4-Aminomethyl-phenylamino)-8-methoxy-4-phenylamino-quinazoline;
Naphthalene-1-sulfonic acid 4-[(4-amino-quinazolin-2-ylamino)-methyl]-benzylamide;

Naphthalene-1-sulfonic acid 3-[(4-amino-quinazolin-2-ylamino)-methyl]-benzylamide;
N-Methyl-[4-(8-methyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide;
N,N-Dimethyl-[4-(8-methyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methane-sulfonamide;
N,N-Dimethyl-[4-(8-methyl-4-methylamino-quinazolin-2-ylamino)-phenyl]-methane-sulfonamide;
N,N-Dimethyl-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methane-sulfonamide;
N(6),N(6)-Dimethyl-N(2),N(4)-diphenyl-quinazoline-2,4,6-triamine;
N(4)-(3-Chlorophenyl)-N(6),N(6)-dimethyl-N(2)-phenyl-quinazoline-2,4,6-triamine;
[4-(6-Dimethylamino-4-phenylamino-quinazolin-2-ylamino)-phenyl]-N,N-dimethyl-methane-sulfonamide;
[4-(8-Dimethylaminomethyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-N,N-dimethyl-methanesulfonamide;
8-Methoxymethyl-N(2)-(4-methoxy-phenyl)-N(4)-phenyl-quinazoline-2,4-diamine;
N(2)-(4-Ethanesulfonylmethyl-phenyl)-8-methoxymethyl-N(4)-phenyl-quinazoline-2,4-diamine;
[4-(8-Methoxymethyl-4-phenylamino-quinazolin-2-ylamino-phenyl]-N-methyl-methanesulfonamide;
N(2)-(4-Ethansulfonylmethyl-phenyl)-8-methoxy-N(4)-phenyl-quinazoline-2,4-diamine;
N(4)-Cyclopropyl-N(2)-(4-ethansulfonylmethyl-phenyl)-8-methoxy-quinazoline-2,4-diamine;
N(4)-Cyclopropylmethylamino-N(2)-(4-ethansulfonylmethyl-phenylamino)-quinazoline;
N(2)-(4-Ethansulfonylmethyl-phenyl)-N(4)-methyl-quinazoline-2,4-diamine;
N(4)-(2-Dimethylamino-ethyl)-N(2)-(4-ethanesulfonylmethyl-phenyl)-quinazoline-2,4-diamine;
{4-[4-(3-Chlorophenylamino)-quinazolin-2ylamino]-phenyl}-N,N-dimethyl-methanesulfonamide;
[(4-Methoxyphenyl)-(4-phenylamino-quinazolin-2-yl)amino]-acetic acid ethyl ester;
[{2-[4-(2-methoxyethoxy)-phenylamino]-quinazolin-4-yl-(4-methoxyphenyl)amino]-acetic acid ethyl ester;
N(4)-Cyclohexyl-N(4)-ethyl-N(2)-[4-(methoxyethoxy)-phenyl-quinazoline-2,4-diamine;
[4-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-quinazolin-2-yl]-[4-(2-methoxyethoxy)phenyl]amine;
2-[4-(Benzoylamino-methyl)-phenylamino]-4-phenylamino-quinazoline;

2-[4-(Amino-carbonyl)-phenylamino]-4-phenylamino-quinazoline;

2-[4-(2-Hydroxy-ethyl)-phenylamino]-4-phenylamino-quinazoline;

2-[4-(2-Hydroxy-ethyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;

2-[4-(2-Hydroxy-ethyl)-phenylamino]-8-methoxy-4-phenylamino-quinazoline;

2-[4-(2-Methoxy-ethyl)-phenylamino]-4-phenylamino-quinazoline;

2-[4-(2-Methoxy-ethyl)-phenylamino]-4-(4-amino-carbonyl-phenylamino)-quinazoline;

2-[4-(2-Methoxy-ethyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;

2-[4-(3-Hydroxy-propyl)-phenylamino]-8-methoxy-4-phenylamino-quinazoline;

2-[4-(3-Hydroxy-propyl)-phenylamino]-4-phenylamino-quinazoline;

2-[4-(3-Hydroxy-propyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;

2-[4-(3-Hydroxy-propyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;

2-[4-(2-Hydroxy-ethoxy)-phenylamino]-4-phenylamino-quinazoline;

2-[4-(2-Hydroxy-ethoxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;

2-[4-(2-Hydroxy-ethoxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;

2-[4-(2-Methoxy-ethyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;

2-[4-(3 2-[4-(3-Hydroxy-propyl)-phenylamino]-4-cyclohexylamino-quinazoline;

2-[4-(3-Ethyl-4-methoxy)-phenylamino]-4-phenylamino-quinazoline;

2-[4-(3-Hydroxy-propyl)-phenylamino]-4-cyclohexylamino-quinazoline;

4-(4-Chloro-phenylamino)-2-[4-(methoxy-acetylamino-methyl)-phenylamino]-8-methoxy-quinazoline;

4-(4-Fluoro-phenylamino)-8-methoxy-2-[4-(2-hydroxyethyl)-phenylamino]-quinazoline;

2-[4-(3-Hydroxy-propyl)-phenylamino]-4-(3-methyl-phenylamino)-quinazoline;

2-[4-(3-Hydroxy-propyl)-phenylamino]-4-(3-hydroxyl-phenylamino)-quinazoline;

6-Chloro-4-cyclohexylamino-2-[4-(3-hydroxy-propyl)-phenylamino]-quinazoline;

6-Chloro-4-cyclohexylamino-2-[4-(2-hydroxy-ethoxy)-phenylamino]-quinazoline;

2-[4-(3-Ethoxy-propoxy)-phenylamino]-4-phenylamino-quinazoline;

6-Fluoro-2-[4-(3-hydroxy-propyl)-phenylamino]-4-(3-methyl-phenylamino)-quinazoline;

2-[4-(3-Benzyloxy-propoxy)-phenylamino]-4-phenylamino-quinazoline;

2-[4-(3-Benzyloxy-propoxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;

2-[4-(2-Methoxy-ethoxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;

4-Cyclohexylamino-2-[4-(3-benzyloxy-propoxy)-phenylamino]-quinazoline;

2-[4-(2-Methoxy-ethoxy)-phenylamino]-4-(3-hydroxy-phenylamino)-quinazoline;

2-[4-(2-Methoxy-ethoxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;

4-Cyclohexylamino-2-[4-(3-hydroxy-propoxy)-phenylamino]-quinazoline;
4-Cyclohexylamino-2-(4-hydroxy-phenylamino)-quinazoline;
4-Cyclohexylamino-2-[4-(2-methoxy-ethoxy)-phenylamino]-8-methoxy-quinazoline;
4-(4-Chloro-phenylamino)-2-[4-(2-methoxy-ethoxy)-phenylamino]-8-methoxy-quinazoline;
4-(4-Fluoro-phenylamino)-2-[4-(2-methoxy-ethoxy)-phenylamino]-8-methoxy-quinazoline;
4-Cyclohexylamino-2-[4-(2-methoxy-ethoxy)-phenylamino]-quinazoline;
4-N-Ethyl-cyclohexylamino-2-[4-(2-methoxy-ethoxy)-phenylamino]-8-methoxy-quinazoline;
4-(4-Chloro-phenylamino)-2-[4-(2-methoxyacetyl-aminomethyl)-phenylamino]-8-methoxy-quinazoline;
4-Cyclohexylamino-8-methoxy-2-(4-phenylamino)-quinazoline;
2,4-Di-(4-chloro-phenylamino)-quinazoline;
2-[4-(2-Methoxyacetyl-aminomethyl)-phenylamino]-8-methoxy-4-phenylamino-quinazoline;
4-Cyclohexylamino-2-[4-(2-hydroxyethyl)-phenylamino]-quinazoline;
2-[4-Aminomethyl)-phenylamino]-4-(4-chloro-phenylamino)-8-methoxy-quinazoline;
2-[4-(3-Hydroxy-propoxy)-phenylamino]-4-(3-methyl-phenylamino)-quinazoline;
4-Cyclohexylamino-2-[3,4-(methylene-dioxo)-phenylamino]-8-methoxy-quinazoline;
2-[3,4-(Methylene-dioxo)-phenylamino]-8-methoxy-4-phenylamino-quinazoline;
4-(4-Fluoro-phenylamino)-2-[3,4-(methylene-dioxo)-phenylamino]-8-methoxy-quinazoline;
4-(3-Hydroxy-phenylamino)-2-[4-(piperidin-1-yl)-phenylamino]-quinazoline;
4-(3-Methyl-phenylamino)-2-[4-(3-benzyloxy-propoxy)-phenylamino]-quinazoline;
2-[4-(2-Acetoxy-ethyl)-phenylamino]-4-phenylamino-quinazoline;
4-[6-1(H)-Indazol-amino]-2-(4-methoxy-phenylamino)-quinazoline;
4-Cyclohexylamino-2-[4-(2-acetoxy-ethyl)-phenylamino]-quinazoline;
4-Cyclohexylamino-2-[4-(3-pivaloyloxy-propoxy)-phenylamino]-quinazoline;
(S)-2-(4-Methoxy-phenylamino)-4-(1-phenyl-ethylamino)-quinazoline; 4-(4-Chloro-phenylamino)-2-[(2-hydroxy-ethoxy)-phenylamino]-8-methoxy-quinazoline;
8-Acetoxy-4-(4-chloro-phenylamino)-2-[(2-methoxy-ethoxy)-phenylamino]-quinazoline;
4-Cyclohexylamino-2-(4-chloro-3-methoxy-phenylamino)-8-methoxy-quinazoline; and
4-(4-Chloro-3-methoxy-phenylamino)-2-(4-methoxy-phenylamino)-quinazoline; or, in each case, a salt thereof.

11. A pharmaceutical composition for the treatment and prophylaxis of diseases or disorders associated with NPY Y5 receptor subtype comprising a therapeutically effective

amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1.
and a carrier.

12. A pharmaceutical composition according to claim 11 for the treatment of disorders or disease states caused by eating disorders, of obesity, bulimia nervosa, diabetes, dyspilipidimia, hypertension, memory loss, epileptic seizures, migraine, sleep disturbance, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion or diarrhea.

13. A method for the treatment and prophylaxis of diseases or disorders associated with NPY Y5 receptor subtype comprising administering to a warm-blooded animal, including man, in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1.

INTERNATIONAL SEARCH REPORT

Internati . Application No
PCT/EP 96/05066

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/95 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 064 833 A (IFE ET. AL.) 12 November 1991 see claims; examples ---	9
X	EP 0 326 329 A (ELI LILLY & CO.) 2 August 1989 see examples 1,7,24-28,74 ---	9
X	WO 92 14716 A (PFIZER INC.) 3 September 1992 see claims; examples ---	9
X	WO 95 25726 A (RECORDATI S.A. CHEMICAL AND PHARMACEUTICAL CO.) 28 September 1995 see claims; example 28 ---	9
X	WO 92 07844 A (PFIZER INC.) 14 May 1992 see claims; examples 1-71 ---	9
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
5 May 1997	23.05.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Helps, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/05066

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 225 866 A (GEROT PHARMAZEUTIKA GMBH) 16 June 1987 see example 2	9
X	WO 94 14795 A (YUHAN CORPORATION) 7 July 1994 see claims; examples 18-61	9
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 24, no. 2, February 1981, WASHINGTON DC, US, pages 127-40, XP000653661 E. F. ELSLAGER ET. AL.: "Synthesis and Antimalarial Effects of N2-Aryl-N4-[(dialkylamino)alkyl]- and N4-Aryl-N2-[(dialkylamino)alkyl]-2,4-quinazolinediamines." see tables II,,III,,IV	9
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 28, no. 1, January 1985, WASHINGTON DC, US, page 12-17 XP000653640 J. MILLEN ET. AL.: "2-(beta-Arylethylamino)- and 4-(beta-Arylethylamino)quinazolines as Phosphodiesterase Inhibitors." see page 16, column 2, paragraph 4	9
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, no. 6, June 1993, WASHINGTON DC, US, pages 690-8, XP000652149 D. GIARDINA ET. AL.: "Structure-Activity Relationships in Prazosin-Related Compounds. 2. Role of the Piperazine Ring on alpha-Blocking Activity." see table 1	9
A	EP 0 448 765 A (HEUMANN PHARMA GMBH) 2 October 1991 see whole document	1-13
A	EP 0 614 911 A (ELF SANOFI) 14 September 1994 see whole document	1-13
P,A	WO 96 12489 A (ELI LILLY & CO.) 2 May 1996 see claims; examples	1-13

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 96/05066

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 13
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-13
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

In view of the very broad scope of the claims which include vague definitions such as "heterocyclic aryl" and "substituted amino", the search has been limited to the scope covered by the examples on economic grounds. Some of the compounds in claim 10 are not included in the scope of claim 9.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 96/05066

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5064833 A	12-11-91	AU 627576 B	27-08-92
		AU 5486490 A	15-11-90
		CA 2015981 A	10-11-90
		DE 69003465 D	28-10-93
		DE 69003465 T	20-01-94
		EP 0404322 A	27-12-90
		JP 3017068 A	25-01-91
EP 326329 A	02-08-89	AU 632994 B	21-01-93
		AU 2874789 A	03-08-89
		CN 1035825 A	27-09-89
		DK 170817 B	29-01-96
		EG 19187 A	30-10-94
		JP 1226877 A	11-09-89
		PT 89506 B	29-04-94
		US 5411963 A	02-05-95
WO 9214716 A	03-09-92	AT 121735 T	15-05-95
		AU 655798 B	12-01-95
		AU 1184892 A	15-09-92
		BR 9205645 A	07-06-94
		CA 2101542 A	21-08-92
		CN 1064271 A	09-09-92
		CZ 9203872 A	13-04-94
		DE 9290018 U	14-10-93
		DE 69202243 D	01-06-95
		DE 69202243 T	31-08-95
		EP 0572437 A	08-12-93
		ES 2071484 T	16-06-95
		HU 64755 A	28-02-94
		JP 6500117 T	06-01-94
		ZA 9201911 A	19-08-93
WO 9525726 A	28-09-95	AU 1894895 A	09-10-95
		EP 0750614 A	02-01-97
		ZA 9502208 A	28-12-95
WO 9207844 A	14-05-92	AT 124694 T	15-07-95
		AU 644035 B	02-12-93
		AU 9059291 A	26-05-92

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 96/05066

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9207844 A		BR 9107070 A	31-05-94
		CA 2095213 A	07-05-92
		CN 1061411 A	27-05-92
		DE 9190155 U	07-10-93
		DE 69111077 D	10-08-95
		DE 69111077 T	02-11-95
		EP 0556310 A	25-08-93
		ES 2074867 T	16-09-95
		FI 932032 A	05-05-93
		HU 64533 A	28-01-94
		NZ 240476 A	27-04-94
		SK 400992 A	09-08-95
		US 5444062 A	22-08-95
		ZA 9108767 A	05-05-93
EP 225866 A	16-06-87	AT 384218 A	12-10-87
		DE 3681701 A	31-10-91
		JP 62132869 A	16-06-87
		US 4795750 A	03-01-89
WO 9414795 A	07-07-94	EP 0677049 A	18-10-95
		JP 8500841 T	30-01-96
EP 448765 A	02-10-91	AT 109979 T	15-09-94
		AU 637882 B	10-06-93
		CA 2037433 A	01-10-91
		DE 59006842 D	22-09-94
		IE 65252 B	18-10-95
		IL 97424 A	26-05-95
		JP 7089939 A	04-04-95
EP 614911 A	14-09-94	FR 2701480 A	19-08-94
		AU 673398 B	07-11-96
		AU 5516594 A	18-08-94
		CA 2115631 A	16-08-94
		CN 1104634 A	05-07-95
		FI 940680 A	16-08-94
		HU 66960 A	30-01-95
		JP 6293794 A	21-10-94
		NO 940503 A	16-08-94

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 96/05066

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 614911 A		NZ 250878 A	27-02-96
		US 5506258 A	09-04-96
		ZA 9401029 A	15-08-95
WO 9612489 A	02-05-96	AU 3953795 A	15-05-96
		EP 0716854 A	19-06-96